Endo-Selective Epoxide-Opening Cascades in Water

by

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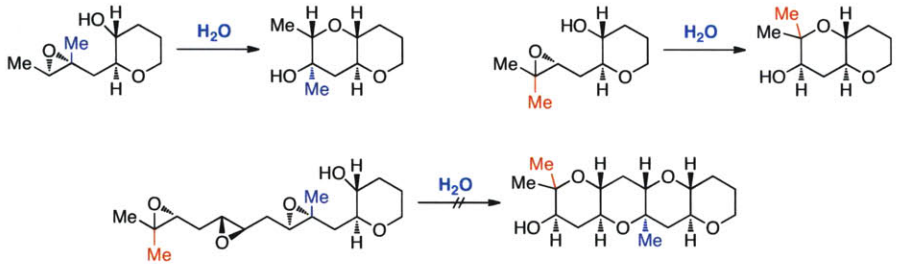
ABSTRACT

Chapter I. Introduction to the Ladder Polyethers.

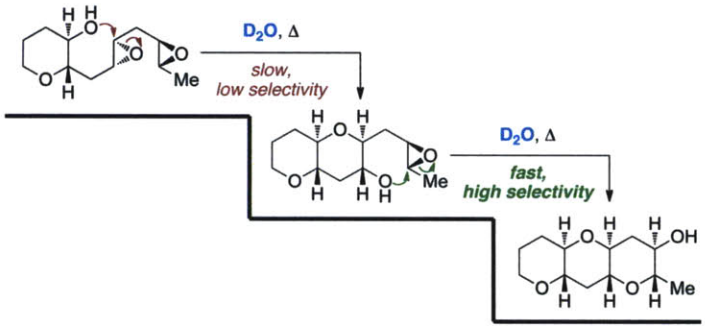
We introduce the bioactivity of the ladder polyether natural products and provide an overview of the puzzle that is their biogenesis. Cascades of *endo*-selective epoxide opening inspired by the biosynthetic proposal and promoted by simple neutral water can provide efficient access to these compounds.

Chapter II. Water-Promoted Epoxide Opening Accommodates Methyl Substitution.



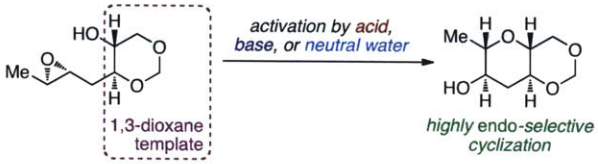
Methyl (Me) substitution poses a challenge to the achievement of *endo*-selective epoxide-opening cascades, as these groups can direct the regioselectivity of epoxide opening. Water as reaction solvent and promoter overcomes such directing effects and enables the incorporation of proximally Me-substituted epoxides into *endo*-selective cascades. However, Me-substituted epoxides do reduce the overall efficiency of cascades.

Chapter III. Kinetics of an Epoxide-Opening Cascade Promoted by Neutral Water. Evidence for a Stepwise Mechanism.



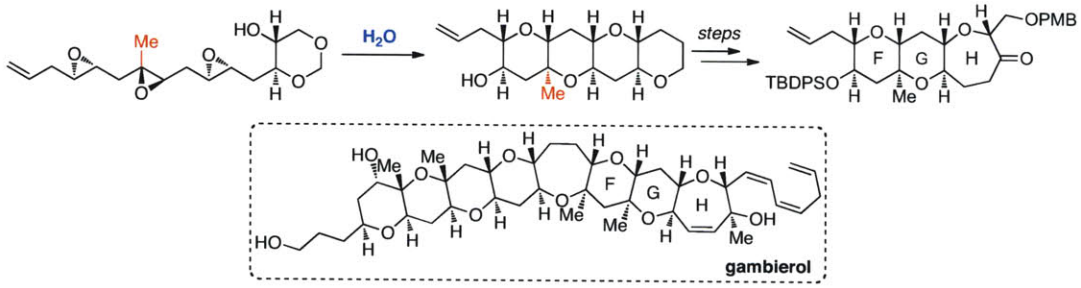
Detailed investigation of the kinetics of an *endo*-selective epoxide-opening cascade in water reveals a stepwise mechanism, not a concerted one. While the first step proceeds with poor rate and selectivity, the second cyclization, which is templated by a fused THP diad, proceeds with excellent *endo* selectivity.

Chapter IV. Preliminary Investigation of a Dioxane Template for *Endo*-Selective Epoxide-Opening Cyclization.



Use of a 1,3-dioxane as template ring, a methylene acetal engenders *endo*-selective epoxide opening under both acidic and basic conditions. Cyclization in neutral water proceeds with superb *endo* selectivity.

Chapter V. Progress Toward the Synthesis of Gambierol via *Endo*-Selective Epoxide-Opening Cascades Promoted by Water.



We report progress toward the biomimetic total synthesis of the ladder polyether gambierol. The *FGH* ring system has been synthesized in a 20 step longest linear sequence, via an *endo*-selective epoxide-opening cascade promoted by water.

Chapter VI. Conclusion: Potential Implications of the Foregoing Work on the Biosynthesis of the Ladder Polyethers.

We summarize lessons learned from *in vitro* emulation of the hypothesized biosynthesis of the ladder polyethers and speculate on the possibility of ring junction methylation subsequent to the epoxide-opening cascade step.

Thesis Supervisor: Timothy F. Jamison
Title: Professor of Chemistry

Preface

Portions of this thesis have appeared in the following articles that were co-written by the author:

Water Overcomes Methyl Group Directing Effects in Epoxide-Opening Cascades.
Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678.

New Strategies for the Stereocontrolled Synthesis of Substituted "Skipped" Diepoxides.
Morten, C. J.; Jamison, T. F. *Tetrahedron* **2009**, *65*, 6648.

The Development of Endo-Selective Epoxide-Opening Cascades in Water.
Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F.
Chem. Soc. Rev. **2009**, *38*, 3175.

Evidence That Epoxide-Opening Cascades Are Stepwise and Become Faster and More Selective After the First Cyclization.
Morten, C. J.; Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2011**, *133*, 1902.

Acknowledgements

I must first thank my advisor, Professor Timothy F. Jamison, for his continued guidance, support, and forbearance. From my first weeks at MIT in Tim's tutorial section, I've been inspired by his wide-ranging enthusiasm for all aspects of organic chemistry. Tim sold me on the study of water-promoted epoxide-opening by describing it simply as that, as organic chemistry, rather than as a more narrowly defined problem of synthesis, method development, or mechanistic investigation. I walked out of one our early meetings with papers on both polyketide biosynthesis and Ti–alkyne complexes, and I recall thinking that there was a lot to learn in between. The project has proved fascinating and challenging in equal measure. It's been a true privilege to work on. I'm tremendously grateful for the freedom that Tim has given me (and all of his co-workers) to follow my curiosity down a few dead ends and, in the process, to grow as an independent scientist.

I must acknowledge Professor Stephen Buchwald for his support and for serving as chair of my thesis committee. I also thank Professor Rick Danheiser and Professor Sarah O'Connor for helpful discussions over the years.

The Jamison group is an unusually collegial bunch, and it's been a pleasure to count myself a member for the last four and a half years. I'm especially indebted to those who helped me get up to speed in my first years in the group. Dr. Ivan Vilotijevic very generously welcomed me onto the project and taught me the details of the biogenesis and bioactivity of the ladder polyethers. Dr. Aaron Van Dyke first showed me how to identify and isolate an *endo* cascade product from a heap of *exo* chaff, convinced me (and the group) of the utility of "artificial" acetal templates, and later got me started on the synthesis of gambierol. Dr. Sze-Sze Ng was superhuman in her talent and kindness. Dr. Brian Underwood helped me run my first Shi epoxidation and filled many, many hours in lab with conversation and camaraderie. Dr. Jeff Byers and I have worked and conversed with each other for several years now, which has been a joy and an honor. I have benefited enormously from the incredible depth of his knowledge and also from his endless, pestering stream of questions. I must particularly thank him for agreeing to collaborate on a study of the mechanism of an epoxide-opening cascade in water and for guiding me through the rigors of kinetic analysis.

I've had the pleasure of working alongside some other talented scientists in the investigation of epoxide-opening cyclization. Jessica Tanuwidjaja, who joined the group soon after me, is a walking encyclopedia on the synthesis and reactions of epoxides. Her tenacity and intelligence are impressive (and motivated me to try to keep up). Dr. Denise Colby was master planner of our group's approach to gambierol, which has been a thrill to be a part of, and also a great mentor. Fate played a cruel trick on Pat Sittihan by giving him both a desk and a hood next to mine, but he's weathered this misfortune graciously. His dedication is admirable, and with him, Tamara Halkina, and Sarah Tasker (two of the group's remarkably talented trio of first year students) in charge, the project is in good hands.

To many others in Jamison group (Dr. Neil Langille, Dr. Jim Trenkle, Kate Woodin, Dr. Jason Ho, Dr. Victor Gehling, Dr. Hiro Ohmiya, Brian Sparling, Dr. Lukas Brändli, Yuta Nishina, Ngan Nguyen, Azusa Kondoh, Nikolas Huwyler, Dr. Yutaka Ikeuchi, Dr. Alessandro Agosti, David Tong, Dr. Andrew Lauer, Dr. Megan Foley, Dr. Matt Bedore, Dr. Kristin Schleicher, Dr. Thomas Steinlin, Dr. Adam Sniady, Dr. Ryosuke Matsubara, Kurt Armbrust, Dr. Andreas Tschöp, Dr. Damien Webb, Dr. Andrew Leduc, Dr. Prakash Palde, Dr. Bo Shen, Dr. Alicia Gutierrez, Dr. Matthew Grant Beaver, Dr. Andy Kleinke, Dr. Kang-sang Lee, Dr. Jenn Kozak, Dr. Yun Zhang, Dr. James Mousseau, Heejin Kim, Eric Standley, and surely other important names that I'm forgetting), I say thanks for your help and insight. Additional appreciation goes to Dr. Alicia Gutierrez for her generous preparation of many grams of $CpRu(NCMe)_3PF_6$, which enabled the synthesis of the *FGH* rings of gambierol. I would also like to acknowledge Dr. Timothy Heffron for initiating the group's exploration into biomimetic synthesis of ladder polyether natural products.

None of the following work would have been possible without the support of the staff of the MIT DCIF, and I especially thank Dr. Jeff Simpson and Dr. Bob Kennedy for help with NMR and Li Li for HRMS. I'm also grateful to Dr. Peter Müller and Dr. Michael Takase of the X-Ray Diffraction Facility for their assistance. I am much obliged to Sara Frenier, Nancy Parkinson, Susan Brighton, Liz McGrath, Fionnuala Coary, and Tyler Brezler for their help over the years.

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My parents, sister, and brother have been absolutely useless at helping me solve problems in my research, but I love them anyway. Finally, I thank Alex for staying with me for five long years, even as graduate school robbed me first of my emotional well-being and then my hair.

Thank you, everyone.

Cambridge, MA
April 2011

Table of Contents

Abbreviations

$[\alpha]_D$	specific rotation at 589 nm (sodium D line)
Ac	acetyl
AD mix	Sharpless asymmetric dihydroxylation mix
Ar	generic aryl substituent
B:	generic base
Bn	benzyl
brsm	based on recovered starting material
BTX	brevetoxin
Bu	butyl
Bz	benzoyl
CAM	ceric ammonium molybdate
cat.	catalyst or catalytic (quantity)
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
d	day(s)
DART	direct analysis in real time
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate
DIAD	diisopropylazodicarboxylate
DIBALH	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMM	dimethoxymethane
DMP	dimethoxypropane
DMPU	1,3-dimethyltetrahydropyrimin-2(1*H*)-one (*N,N'*-dimethylpropyleneurea)
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
E^+	generic electrophile
EDA	ethylenediamine
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
ESI	electron spray ionization
Et	ethyl
GC	gas chromatography
h	hour(s)
HMDS	bis(trimethylsilyl)amine (hexamethyldisilazane)
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
imid	imidazole
*i*Pr	isopropyl
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide (potassium hexamethyldisilazane)
KP_i	potassium phosphate

LA	Lewis acid
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
Mes	2,4,6-trimethylphenyl (mesityl)
min	minute(s)
MOM	methoxymethyl
M.S.	molecular sieves
nBu	n-butyl
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	generic nucleophile
PG	generic protecting group
Ph	phenyl
P_i	phosphate
PIPES	piperazine-*N*,*N*'-bis(2-ethanesulfonic acid)
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PT	5-phenyltetrazole
Pv	trimethylacetate (pivalate)
py	pyridine
R	generic carbon substituent
R_f	retention factor
rr	regioisomeric ratio
SADH	Sharpless asymmetric dihydroxylation
SAM	*S*-adenosylmethionine
Sharpless AE	Sharpless asymmetric epoxidation
Shi AE	Shi asymmetric epoxidation
SiO_2	silica gel
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMANO	trimethylamine-*N*-oxide
TMEDA	*N*,*N*,*N*',*N*',-tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
t_R	retention time
Ts	*para*-toluenesulfonyl (tosyl)
X	generic heteroatom substituent

Chapter I

Introduction to the Ladder Polyethers: Bioactivity, Biosynthesis, and Chemical Synthesis.

A. Ladder polyethers as red tide toxins and probes in chemical biology.

Red tides are a longstanding and global environmental problem. Less evocatively and more rigorously referred to as harmful algal blooms (or "HABs"), these events are sudden, drastic increases in marine algae populations accompanied by the release of massive quantities of toxic compounds into seawater. The consequent death of fish, marine mammals, and other wildlife, sometimes accompanied by human poisoning, can inflict great harm on the environment and economy of coastal regions. In a multidisciplinary enterprise spanning chemistry, biology, ecology, and oceanography, the scientific community continues to study both the long-term and immediate causes of red tides.[1]

Through this effort, a particular group of natural products known as the ladder polyethers has been implicated as the agents responsible for the ill effects of many red tides.[2] Ladder polyether toxins have been recognized in warm-water regions across the globe, from Tahiti and the Caribbean to Vietnam and Japan.[2] As the cause of ciguatera and neurotoxic shellfish poisoning,[3] ladder polyethers are a nearly annual menace to the Gulf Coast of the United States and rank among the most serious threats to the survival of the endangered Florida manatee.[4]

Much remains unknown about red tides and the ladder polyethers. The specific triggers of algal blooms, and to what extent human activity contributes, are a mystery.[5] Furthermore, the exact evolutionary purpose that red tide toxins serve for their producing dinoflagellates is still somewhat mysterious, as the allelopathic effects of the ladder polyethers on predators and competitor autotrophs are only now being illuminated.[3a,6]

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[1] Sellner, K. G.; Doucette, G. J.; Kirkpatrick, G. J. *J. Ind. Microbiol. Biotechnol.* **2003**, *30*, 383.
[2] (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7182.
[3] (a) Poulson, K. L.; Sieg, R. D.; Kubanek, J. *Nat. Prod. Rep.* **2009**, *26*, 729. (b) Landsberg, J. H. *Rev. Fish Sci.* **2002**, *10*, 113.
[4] Schrope, M. *Nature* **2008**, *452*, 24.
[5] Landsberg, J. H.; Flewelling, L. J.; Naar, J. *Harmful Algae* **2009**, *8*, 598.
[6] (a) Smayda, T. J. *Limnol. Oceanogr.* **1997**, *42*, 1137. (b) Legrand, C.; Rengefors, K; Fistarol, G. O.; Granell, E. *Phycologia* **2003**, *42*, 406. (c) Kubanek, J.; Hicks, M. K.; Naar, J.; Villareal, T. A. *Limnol. Oceanogr.* **2005**, *50*, 883. (d) Kubanek, J.; Snell, T. W.; Pirkle, C. *Limnol. Oceanogr.* **2007**, *52*, 1026. (e) Prince, E. K.; Myers, T. L.; Kubanek, J. *Limnol. Oceanogr.* **2008**, *53*, 531.

However, a good deal has been determined about the extraordinary toxic effects of ladder polyethers on higher vertebrates. Among the ladder polyethers are some of the most potent poisons known, including maitotoxin (**8**, Figure 1), whose murine LD_{50} of 50 ng/kg makes it the single most toxic nonbiopolymeric substance.[7] The toxicity of the ladder polyether poisons arises from their very high affinity for binding to voltage-gated sodium, calcium, or potassium ion transport channel proteins. These proteins span the cellular membrane and mediate the delivery of ions into and out of the cell, a critical role. In cases of ciguatera poisoning and in neurotoxic shellfish poisoning, ladder polyethers act as agonists that bind to sodium channels and induce an influx of ions into cells, thereby causing membrane depolarization.[3] As sodium transport channels are especially important in nerve function (see below), these compounds disrupt the nervous system in particular and lead to neurological damage, and occasionally death.

Ion transport proteins are notoriously difficult to isolate from cell membranes for crystallization and study, and ladder polyethers have therefore proven valuable as selective probes of ion transport channel structure and function.[8] Understanding ion channels may in turn shed light on processes important to human health. For example, sodium ion transport channel proteins are responsible for signal transduction along neurons, making them the basis of nervous system function. Defective ion transport proteins cause a wide range of diseases, including cystic fibrosis, myotonic muscular dystrophy, and erythromelalgia. Increased ion transport channel activity has also been implicated in the metastasis of cancer.[9]

In recent years, the scientific community has just begun to scratch the surface of the chemical biology of the ladder polyethers. For instance, the ladder polyether brevenal (**3**, Figure 1) was first isolated in 2005 and has already shown promise as a tool for studying cystic fibrosis, a disease of overactive voltage-gated sodium ion transport

---

[7] (a) Takahashi, M.; Ohizumi, Y.; Yasumoto, T. *J. Biol. Chem.* **1982**, *257*, 7287. (b) Yokoyama, A.; Murata, M.; Oshima, Y.; Iwashita, T.; Yasumoto, T. *J. Biochem.* **1988**, *104*, 184. (c) Murata, M.; Naoki, H.; Matsunaga, S.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1994**, *116*, 7098. (d) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293.

[8] For a few selected examples, please see: (a) Baden, D. G.; Bourdelais, A. J.; Jacocks, H.; Michelliza, S.; Naar, J. *Environ. Health Perspect.* **2005**, *113*, 621. (b) Matile, S.; Nakanishi, K. *Angew. Chem. Int. Ed.* **1996**, *35*, 757. (c) Ghiaroni, V.; Sasaki, M.; Fuwa, H.; Rossini, G. P.; Scalera, G.; Yasumoto, T.; Pietra, P.; Bigiani, A. *Toxicol. Sci.* **2005**, *85*, 657.

[9] Fiske, J. L.; Fomin, V. P.; Brown, M. L.; Duncan, R. L.; Sikes, R. A. *Cancer Metastasis Rev.* **2006**, *25*, 493.

channels.[10] In general, the potency of the ladder polyethers means that these compounds are produced in nature only in microscopic quantities. Isolation is extraordinarily difficult,[2a] which has been a roadblock to further study. Preparation of these compounds by efficient chemical synthesis would therefore represent a useful contribution to the global effort.

B. Structure and chemical synthesis of the ladder polyethers.

It is not merely the profound bioactivities of the ladder polyethers but also their intricate and beautiful structures that have attracted the attention of synthetic organic chemists. We turn now to those structures (Figure 1). There is significant diversity among the ladder polyethers, as well as a few characteristic similarities. Most distinctive are the ladder cores themselves: long sequences of fused cyclic ethers. These may be joined into polycycles of anywhere between four (as in the compact hemibrevetoxin B, (**4**)) and 15 rings (as in the impressive gymnocin B, (**7**)). The size and stereochemical complexity of the ladder polyethers can be staggering; the aforementioned maitotoxin (**8**) is not only the most toxic natural product known but also the single largest, containing some 32 rings spread over 4 separate ladders.[7c]

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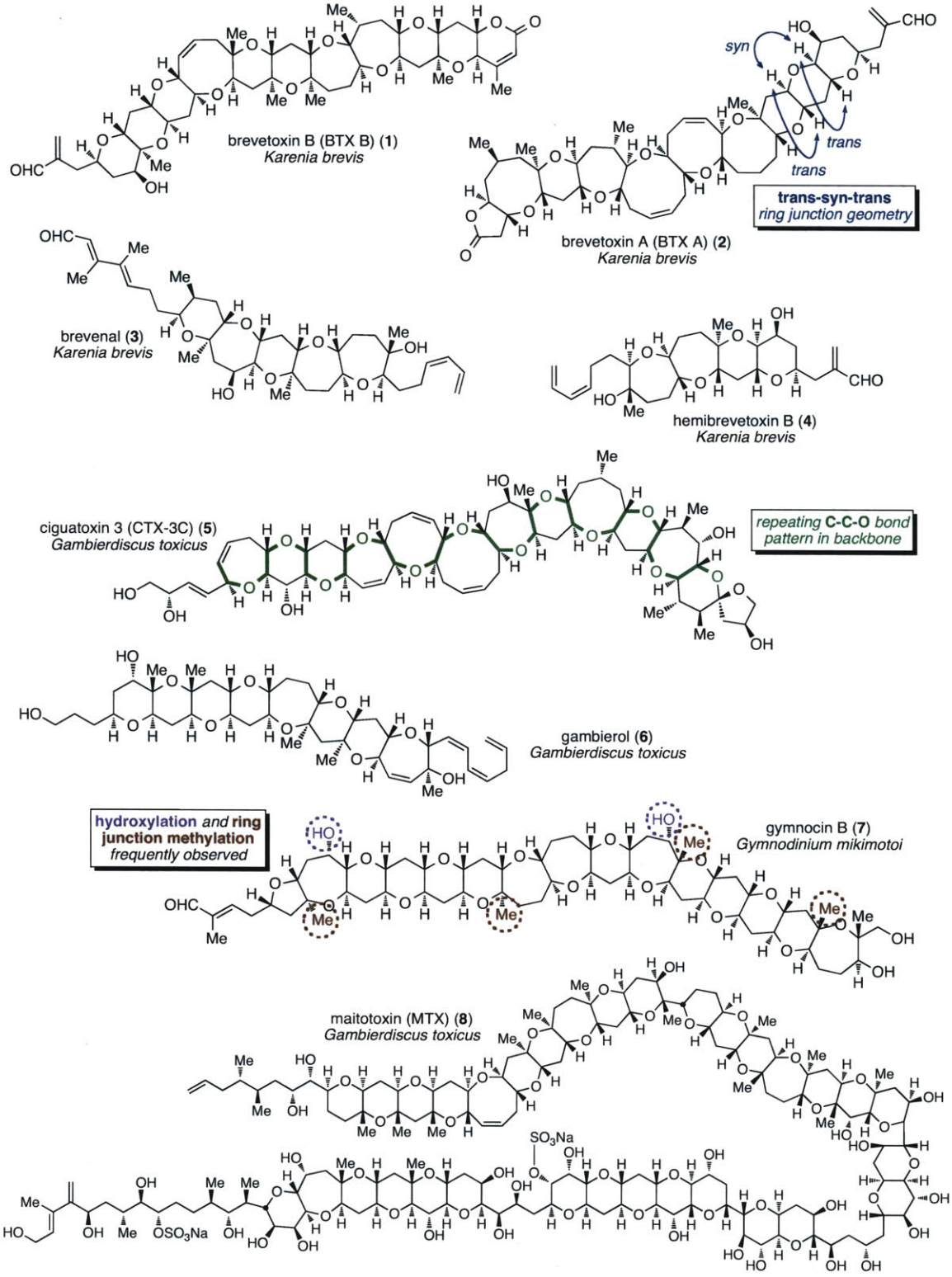
[10] *isolation:* (a) Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M.; Baden, D. G. *J. Nat. Prod.* **2005**, *68*, 2. *structural revision:* (b) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989.
cystic fibrosis studies: (c) Abraham, W. M.; Bourdelais, A. J.; Sabater, J. R.; Ahmed, A.; Lee, T. A.; Serebriakov, I.; Baden, D. G. *Am. J. Respir. Crit. Care Med.* **2005**, *171*, 26.

Figure 1. Structures of selected ladder polyethers. (For each compound, the name of the producing dinoflagellate species is shown in italics.)



While the cyclic ethers that constitute the ladders vary from five-membered tetrahydrofuran (THF) rings to nine-membered oxonanes, six-membered tetrahydropyran (THP) rings are most commonly encountered. With just a single exception,[11] these rings are fused together in a distinctive *trans-syn-trans* geometry (as illustrated in the case of brevetoxin A (**2**)); it is this feature that gives the ladders their remarkable topography and name. Another key structural characteristic of the ladder polyethers is the repeating C—C—O bond pattern that can be traced from one end of the ladder to the other (see ciguatoxin 3 (**5**)). Finally, we note that the ladders are commonly decorated with methyl and hydroxyl substituents (see gymnocin B (**7**)). Methyl groups are often incorporated at ring junctions and are the only substituent other than hydrogen ever observed at ring junctions.

The stereochemical complexity and often intimidating scale of the ladder polyethers have tested the limits of what organic chemistry can accomplish. Indeed, some of these ambitious efforts are now recognized as modern "classics" of total synthesis.[12] As the total synthesis of ladder polyethers has been thoroughly and recently reviewed,[2b,13] we will touch on the subject only briefly. An array of elegant and powerful methods have been invented for construction of six-membered THP rings, seven-membered oxepanes, and eight-membered oxocanes, as well as for their controlled union into *trans-syn-trans*-fused ladders. Almost exclusively, the prevailing emphasis has been on efficient synthesis of one or two rings at a time, via cyclization or annulation steps, and then subsequent convergent assembly of these small ladder fragments into larger units. A diverse set of reactions for ring formation has been described, ranging from samarium(II) iodide-promoted reductive couplings[14] to ring-closing metathesis of enol ethers[15] to alkylative ring-closing etherification reactions.[16]

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[11] The *IJK* ring system of maitotoxin contains a unique *trans-anti-trans*-fused THP triad. For discussion, please see: (a) Gallimore, A. R.; Spencer, J. B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4406. (b) Nicolaou, K. C.; Frederick, M. O. *Angew. Chem. Int. Ed.* **2007**, *46*, 5278. (c) Nicolaou, K. C.; Cole, K. P.; Frederick, M. O.; Aversa, R. J.; Denton, R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 8875.

[12] Nicolaou, K. C.; Sorenson, E. J. *Classics in Total Synthesis*; Wiley VCH: Weinheim, 1996.

[13] (a) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (b) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379. (c) Vilotijevic, I.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 5250.

[14] Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron* **2002**, *58*, 1853., and references therein.

[15] (a) Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2007**, *129*, 12604. (b) Zhang, Y.; Rainier, J. D. *Org. Lett.* **2009**, *11*, 237.

[16] (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1986**, *108*, 2468. (b) Nicolaou, K.

C. Biosynthesis of the ladder polyethers.

The aforementioned iterative synthetic approach to the ladder polyethers is of confirmed utility, as it has resulted in the total synthesis of many of the group's members (including compounds **1-6** in Figure 1). However, iterative, gradual approaches to these massive and stereochemically complex structures have demanded lengthy synthetic efforts, with overall step counts of 100 or more being common.[13a] Nature is proposed to use a strategy that is radically different and arguably much more concise.

The specifics of the biogenesis of the ladder polyethers remain unknown. Perhaps the only certainty is their polyketide origin, confirmed on the basis of seminal carbon labeling and feeding experiments by Nakanishi,[17] Shimizu,[18] and Satake,[19] and subsequent studies from Rein and Van Dolah.[20] Little is known beyond this basic origin of the ladder polyethers' carbon skeletons, and a number of major questions remain unanswered, including how oxygen is incorporated and how the rings are formed.

However, a number of biosynthetic proposals for the ladder polyethers have been advanced. The most widely investigated, and perhaps the most appealing in its elegance, is the cascade hypothesis first presented in the scientific literature in 1985 by Nakanishi.[21,22] In this hypothesis, the fused oxacycle cores of the ladder polyethers are

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C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321.

[17] (a) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855. (b) Lee, M. S.; Qin, G.-w.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234.

[18] Chou, H.-N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184.

[19] Satake, M. *Symposium on the Chemistry of Natural Products (Japan)* **2000**, 42, 259.

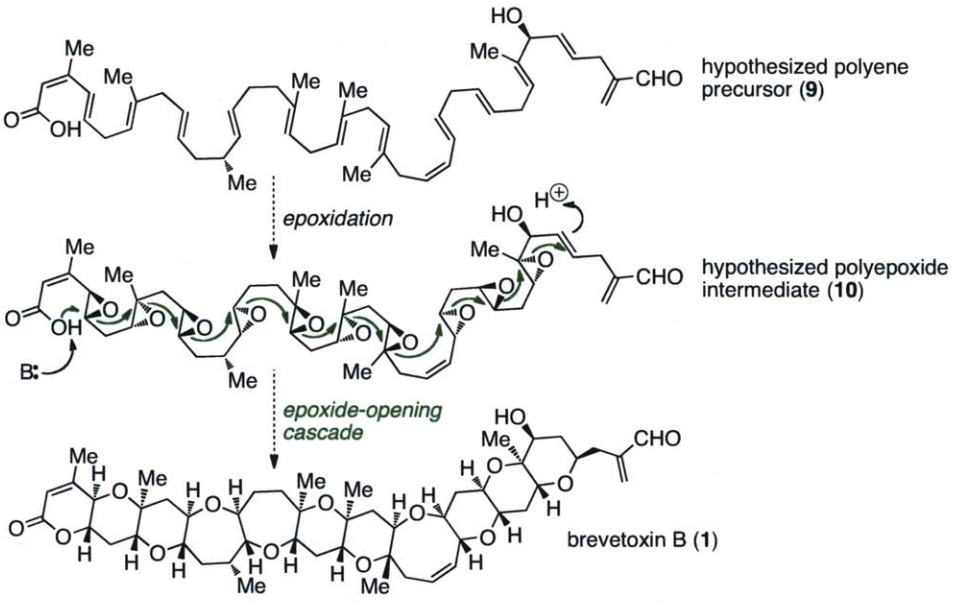
[20] *review:* (a) Kellmann, R.; Stüken, A.; Orr, R. J. S.; Svendsen, H. M.; Jakobsen, K. S. *Marine Drugs* **2010**, *8*, 1011. *original reports:* (b) Snyder, R. V.; Gibbs, P. D. L.; Palacios, A.; Abiy, L.; Dickey, R.; Lopez, J. V.; Rein, K. S. *Mar. Biotechnol.* **2003**, *5*, 1. (c) Snyder, R. V.; Guerrero, M. A.; Sinigalliano, C. D.; Winshell, J.; Perez, R.; Lopez, J. V.; Rein, K. S. *Phytochemistry* **2005**, *66*, 1767. (d) Monroe, E. A.; Van Dolah, F. M. *Protist* **2008**, *159*, 471. (e) Monroe, E. A.; Johnson, J. G.; Wang, Z.; Pierce, R. K.; Van Dolah, F. M. *J. Phycol.* **2010**, *46*, 541.

[21] Nakanishi, K. *Toxicon* **1985**, *23*, 473. In this paper, Nakanishi acknowledges Prof. Robert Thomas as having first suggested an epoxide-opening cascade biosynthesis via private communication.

[22] Conceptually similar prospective biosyntheses were proposed contemporaneously by Shimizu and Nicolaou; see: (a) Shimizu, Y. In *Natural Toxins: Animal, Plant, and Microbial*; Harris, J. B., Ed.; Clarendon: Oxford, 1986; p. 123. (b) Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 588.

proposed to arise from dramatic cascade (or domino) reactions[23] of many epoxide openings, as depicted for the example of brevetoxin B (**1**, Scheme 1).

Scheme 1. Proposed biosynthesis of brevetoxin B (Nakanishi, ref. 21).



Nakanishi's proposal reduces the construction of the imposing brevetoxin B (**1**) to two straightforward steps. First, stereoselective epoxidation of relatively simple polyene **9** provides polyepoxide **10**. Notably, the configuration of every epoxide in **10** is the same, which raises the intriguing possibility that a single (*R*,*R*)-selective epoxidase could catalyze the entire transformation, thereby setting 20 of the natural product's 23 stereocenters.[11a] Subsequently, the key cascade of epoxide-opening cyclizations "zips" polyepoxide **10** into the ladder of **1**. In this proposal, not just one or two rings but rather all eleven rings of brevetoxin B are constructed in a single operation, with no further modification of the product necessary. Interestingly, the distinctive repeating C—C—O bond pattern of the ladder backbone can then be traced back to the three atoms that constitute each epoxide. Moreover, if each epoxide opening proceeds stereospecifically, with inversion of configuration, then the characteristic *trans-syn-trans* geometry of ring fusion can be said to stem from the conservation of (*R*,*R*)-epoxide configuration.

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[23] (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.

The cascade proposal remains highly appealing despite very limited experimental evidence in its favor. Despite significant effort, no polyene or polyepoxide intermediates have ever been isolated from the dinoflagellates that produce ladder polyethers, nor have any epoxide hydrolase enzymes been conclusively identified.[24]

D. Biosynthetic hypothesis as inspiration to synthetic chemists.

As investigation into the biosynthesis of the ladder polyethers continues, synthetic chemists have drawn inspiration from the cascade proposal. Cascade reactions in general are increasingly important in organic synthesis, as they compress multiple elementary reactions into a single operation.[23] In so doing, they reduce the need for wasteful and time-consuming workup and purification steps, improving step economy[25] and atom economy.[26] The proposed two-step transformation of polyene **9** into brevetoxin B (**1**) is remarkably efficient. *In vitro* emulation of this proposal could dramatically streamline the synthesis of the ladder polyethers and potentially make available much greater quantities of these compounds for further study of their chemical biology.

Emulation of the epoxidation step is now possible with a variety of methods for the asymmetric epoxidation of isolated alkenes, perhaps most notably Shi's.[27] Mimicking a cascade of many regioselective epoxide-opening cyclizations like that from **10** to **1** remains a major challenge, however. In fact, achieving good yield in even a single epoxide-opening cyclization of the sort contained in the biosynthetic hypothesis has been a longstanding problem. The crux of the challenge is that intramolecular epoxide opening by a pendent nucleophile can proceed through two different pathways that afford

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[24] For an excellent review of what is (and is not) known about ladder polyether biosynthesis, please see: (a) Gallimore, A. R. *Nat. Prod. Rep.* **2009**, *26*, 266. In 2008 Oikawa and Leadlay independently reported the first evidence for an epoxide hydrolase catalyzing an *endo*-selective epoxide-opening cyclization in the biosynthesis of a natural product (lasalocid A, a polyether ionophore of polyketide origin); see: (b) Shichijo, Y.; Migita, A.; Oguri, H.; Watanabe, M.; Tokiwano, T.; Watanabe, K.; Oikawa, H. *J. Am. Chem. Soc.* **2008**, *130*, 12230. (c) Matsuura, Y.; Shichijo, Y.; Minami, A.; Oguri, H.; Watanabe, M.; Tokiwano, T.; Watanabe, K.; Oikawa, H. *Org. Lett.* **2010**, *12*, 2226. (d) Smith, L.; Hong, H.; Spencer, J. B.; Leadlay, P. F. *ChemBioChem* **2008**, *9*, 2967.

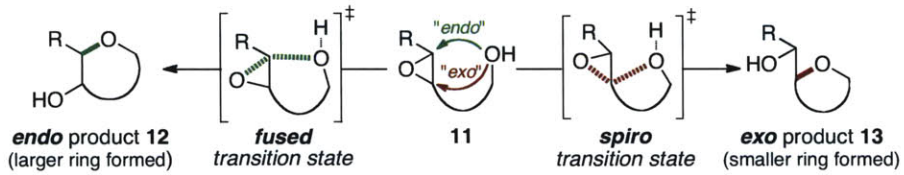
[25] Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*, vol. 2.; Hudlicky, T., Ed.; JAI: Greenwich, 1993; pp 27-66.

[26] Trost, B. M. *Science* **1991**, *254*, 1471.

[27] (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.

regioisomeric products (Scheme 2). Model epoxy alcohol **11** can cyclize to either **12** or **13**. These two pathways are commonly referred to as *endo* and *exo*, respectively, in reference to Baldwin's rules for cyclization.[28,29]

Scheme 2. *Endo* vs. *exo* opening in epoxide-opening cyclization.



The climactic cascade of polyepoxide **10** to **1** requires no fewer than ten *endo* openings (Scheme 1). *Trans*-disubstituted epoxides are by a wide margin the most common variety of epoxide encountered in **10**, as well as in similar putative precursors to other ladder polyethers. Unfortunately for those attempting to mimic the biosynthetic scheme, model cyclizations of simple *trans*-disubstituted epoxides proceed through the spiro or *exo* pathway. A pioneering report from Coxon[30] (Scheme 3) and a raft of examples since[13c] have confirmed that this trend holds for a variety of ring sizes (i.e., 5-*exo* predominates over 6-*endo*, and 6-*exo* over 7-*endo*) and under basic, neutral, and acidic promotion conditions.

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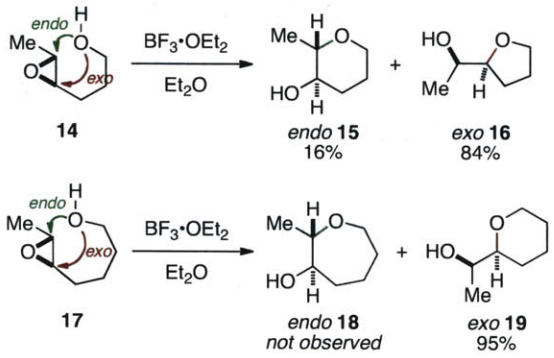
[28] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

[29] Strictly speaking, *endo* and *exo* terminology does not accurately distinguish the two pathways shown in Scheme 2. Because the transition states in both pathways involve breaking a C—O bond that is outside the newly formed ring, both pathways are arguably formally *exo*. A more precise distinction is to designate **12** and **13** as "large ring" and "small ring" products, respectively, rather than as "*endo*" and "*exo*." Correspondingly, the transition states to **12** and **13** should be termed more rigorously as "fused" and "spiro," respectively, rather than as "*endo*" and "*exo*." Regardless, we continue to use the common *endo* and *exo* terminology as it is convenient and thoroughly ingrained in the literature.

[30] Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H. *Aust. J. Chem.* **1973**, *26*, 2521.

Scheme 3. Cyclization of simple *trans*-disubstituted epoxy alcohols (Coxon, ref. 30).



These epoxide-opening cyclizations are kinetically controlled, and in these reactions it seems that the approach required for *endo*-tet cyclization to 6- or 7-membered rings is inaccessibly high in energy, consistent with Baldwin's rules.[31] These are the ring sizes most often required for ladder polyether formation, and so building ladder polyethers from cascades of many (disfavored) *endo* cyclizations would seem to be an impossible task.

However, a number of ingenious methods have been developed to overturn the apparent "intrinsic" *exo* selectivity of simple epoxy alcohol cyclizations. In general, these methods rely on the appendage of a directing group to the epoxide. Such directing groups most commonly act by electronically stabilizing the fused transition state en route to *endo* opening, as in methods developed by Nicolaou,[32] Nakata,[33] McDonald,[34] Morimoto,[35] and Floreancig[36], as well as our own group[37] (Scheme 4). The overwhelming majority of

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[31] In fact, Baldwin points out that the case of opening three-membered rings is unique, as the geometry of the electrophilic center is somewhere between trigonal and tetrahedral. These "not quite tetrahedral" centers generally prefer *exo* opening but are more accommodating than a true tetrahedral center. See ref. 28 and the following reference: Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270.

[32] (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. K.; Somers, P. K. *Chem. Commun.* **1985**, 1359. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (c) Nicolaou, K. C. *Angew. Chem. Int. Ed.* **1996**, *35*, 588.

[33] Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545.

[34] *For selected original reports, see:* (a) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917. (b) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2003**, *5*, 2123. (c) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586. *For accounts, see:* (d) Valentine, J. C.; McDonald, F. E. *Synlett* **2006**, 1816. (e) McDonald, F. E.; Tong, R.; Valentine, J. C.; Bravo, F. *Pure Appl. Chem.* **2007**, *79*, 281.

[35] Morimoto, Y.; Nishikawa, Y.; Ueba, C.; Tanaka, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 810.

[36] Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915.

[37] Uniquely, the TMS group is a competent director for *endo* cyclization under basic activation as well as acidic, suggesting that it serves as more than a carbocation-stabilizing group. For discussion, please see: (a)

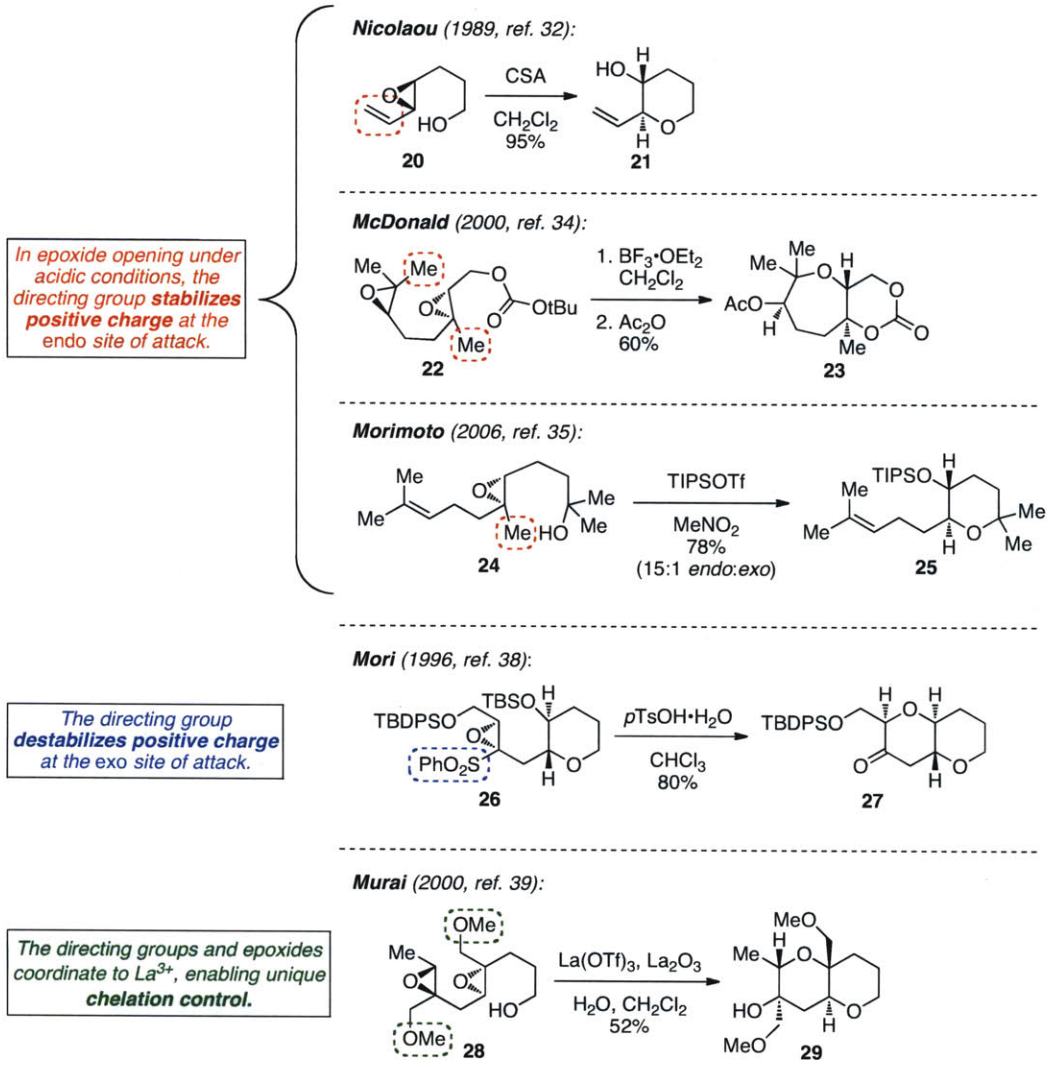
these methods effect cyclization via acidic promotion, either Brønsted or Lewis, to generate epoxonium intermediates. Conversely, a few methods act by destabilizing the spiro transition state en route to *exo* opening, as in the work of Mori[38] and Murai,[39] which also implement acidic promoters. *Endo* cyclization of simple epoxy alcohols under neutral or basic conditions has not been so thoroughly documented,[37c] although there are plentiful examples of *exo* cyclization initiated by base.[13c]

Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339. (b) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056. (c) Heffron, T. P.; Simpson, G. L.; Merino, E.; Jamison, T. F. *J. Org. Chem.* **2010**, *75*, 2681.

[38] (a) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158. (b) Mori, Y.; Furuta, H.; Takase, T.; Mitsuoka, S.; Furukawa, H. *Tetrahedron Lett.* **1999**, *40*, 8019. (c) Furuta, H.; Takase, T.; Hayashi, H.; Noyori, R.; Mori, Y. *Tetrahedron* **2003**, *59*, 9767.

[39] (a) Fujiwara, K.; Tokiwano, T.; Murai, A. *Tetrahedron Lett.* **1995**, *36*, 8063. (b) Fujiwara, K.; Mishima, H.; Amano, A.; Tokiwano, T.; Murai, A. *Tetrahedron Lett.* **1998**, *39*, 393. (c) Fujiwara, K.; Hayashi, N.; Tokiwano, T.; Murai, A. *Heterocycles* **1999**, *50*, 561. (d) Tokiwano, T.; Fujiwara, K.; Murai, A. *Chem. Lett.* **2000**, 272.

Scheme 4. Directing groups for *endo*-selective epoxide-opening cyclization.



In the absence of a directing group on the epoxide, achieving *endo*-selective cyclization has been much more difficult. Notably, McDonald[34] and Floreancig[36] have been able to incorporate one and even two "directing group-free," *trans*-disubstituted epoxides into cascades of epoxonium openings, albeit in lower yield. In a seminal advance, Janda and Lerner developed a catalytic antibody capable of effecting *endo* cyclization of a simple *trans*-disubstituted epoxide,[40] although this method has not seen wide use in synthesis. Jacobsen has reported remarkably *endo*-selective opening of a

[40] Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1993**, *259*, 490.

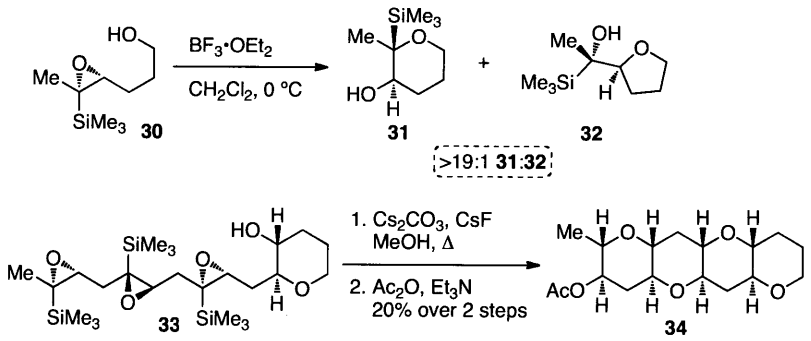
epoxide by a pendent alcohol upon catalysis by a [Co^{III}(salen)] catalyst, but this transformation is limited to cyclization onto monosubstituted epoxides.[41]

Indeed, it appeared that enzymatic control must be required in order to achieve *endo* opening of such substrates, which lack a directing group at the *endo* site of attack. Along these lines, Oikawa and Leadlay have recently shown that the epoxide hydrolase Lsd19 catalyzed an *endo*-selective epoxide-opening cyclization in the biosynthesis of lasalocid.[24b,c,d] Without the enzyme, the substrate cyclizes in the *exo* fashion. Epoxide hydrolases analogous to Lsd19 have not been identified in the dinoflagellates that produce ladder polyethers, but the search is ongoing.[20]

E. *Endo*-selective epoxide-opening cyclization promoted by water and templated by a preformed ring.

Before any investigation of directing group-free epoxide-opening cyclization, the Jamison group developed methods for *endo*-selective epoxide opening guided by a trimethylsilyl (TMS) group at each epoxide. These reports included single-epoxide cyclization promoted by Lewis acid[37a] and a cascade method for ladder synthesis that was base-promoted (Scheme 5).[37b] Notably, these TMS groups act as disappearing directing groups, protiodesilylated *in situ* with the aid of cesium fluoride to afford tetrahydropyran (THP) tetrad **34**, a characteristic subunit of ladder polyether natural products.

Scheme 5. *Endo*-selective epoxide opening directed by TMS groups (Heffron and Jamison, ref. 37).



[41] (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2012.

While TMS groups are exceptional in that they are cleanly removed during the cascade reaction itself, their use as directors had a few shortcomings. Their removal complicated the cascade conditions, as superstoichiometric CsF was required. Moreover, their stereocontrolled introduction made the synthesis of triepoxide **33** rather lengthy. Finally, the installation of a disappearing TMS group at a given position precludes the placement of a methyl group at that site, hindering the incorporation of methyl groups at ring junctions. To avoid some of the limitations associated with these directing groups, and to more closely emulate the Nakanishi hypothesis, we therefore explored whether an *endo*-selective cascade might be possible without them.

An early clue toward what would become the foundation of *endo*-selective epoxide-opening cyclization in the absence of directing groups was revealed by our group's work with TMS-substituted epoxides. Dr. Timothy Heffron observed that preforming a cyclic ether could dramatically improve regioselectivity in subsequent cyclization. Specifically, he compared linear epoxy alcohol **35** to substrate **38**, in which one THP ring has already been formed, and found that **38** cyclized with much higher *endo* selectivity under basic activation (Scheme 6).[42] This remarkable result was the first hint in our group at the power of a *template effect.*[43] Appealingly, the template in this case is not a heavily engineered, "artificial" moiety that must be altered after cyclization; rather, the THP template is a basic subunit of the natural products themselves.

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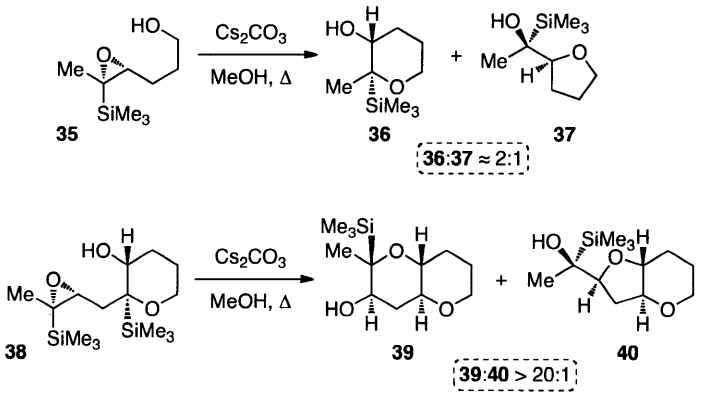
[42] Heffron, T. P. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 2005.

[43] In several important respects, the discovery that THP rings can template 6-*endo* epoxide-opening cyclization was prefigured by Bartlett's 1986 report of 6-*endo* iodonium-opening cyclization templated by a cyclohexane ring. Bartlett showed that such a template overturns the *exo* selectivity normally encountered in cyclizations onto electronically "unbiased," *trans*-disubstituted iodonium cations. Please see: Bartlett, P. A.; Ting, P. C. *J. Org. Chem.* **1986**, *51*, 2230.

Scheme 6. Early suggestions of a template effect (Heffron and Jamison, ref 42).



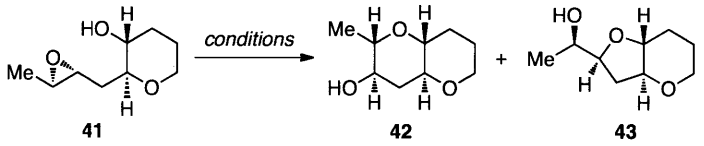
These results illuminated what, in retrospect, is perhaps a rather established fact: pre-organization of a substrate can accelerate an intramolecular reaction and, more important in our case, potentially alter its regioselectivity. We will herein use the term "template" to describe an appended molecular architecture that induces otherwise atypical reactivity and/or selectivity. We surmised that in the case of epoxide-opening cyclization, the template (the preformed THP ring in **38**) could serve to bring the reactive partners, epoxide and alcohol, closer together. In so doing, it could reduce the activation barriers to cyclization, improving rate. It could also alter the relative energies of the *endo* and *exo* transition states; preformation of a THP template ring could conceivably engender more "product-like" transition states, wherein the greater stability of the six-membered ring product over the five would be reflected.

Dr. Ivan Vilotijevic in our group was the first to show that use of a THP template induces high *endo* selectivity in the opening of an epoxide that lacks any kind of steric or electronic directing group (Table 1).[44] This remarkable effect enables *endo* opening of *trans*-disubstituted epoxide **41**. Deionized water was the best promoter discovered, inducing 10:1 selectivity in favor of the desired *endo* product **42** (entry 1). Small alcohols methanol and ethylene glycol were also effective promoters, at least in terms of regioselectivity (entries 2 and 3), although the rate of cyclization was much lower. Strong, more traditional acidic and basic promoters were far less effective (entries 4-6). Indeed, Dr. Vilotijevic showed that *neutral* water was the best promoter for the

[44] Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189.

cyclization of **41**. The peak *endo* selectivity of about 10:1 was observed at pH 7, and selectivity plummeted on moving into acidic or basic solution.[45]

Table 1. Cyclization of templated epoxy alcohol **41** (Vilotijevic and Jamison, ref. 44).

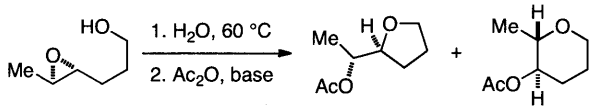


41 **42** **43**

entry	*conditions*	T (°C)	**42:43**
1	deionized H_2O	rt or 60	>10:1
2	ethylene glycol	rt	9:1
3	MeOH	rt	8:1
4	Cs_2CO_3, MeOH	rt	1:2.7
5	BF_3•OEt_2, CH_2Cl_2	-78 to rt	1.4:1
6	AcOH, PhMe	rt	1.6:1

Thus there appears to be a synergistic relationship between the THP template and neutral water as solvent and reaction promoter. Further evidence of this synergy was recently presented by Qu, who determined that *exo* cyclization predominates in neutral water in the absence of a THP template (Scheme 7).[46]

Scheme 7. *Exo*-selective cyclization of linear epoxy alcohol **33** promoted by neutral water (Qu, ref. 46).



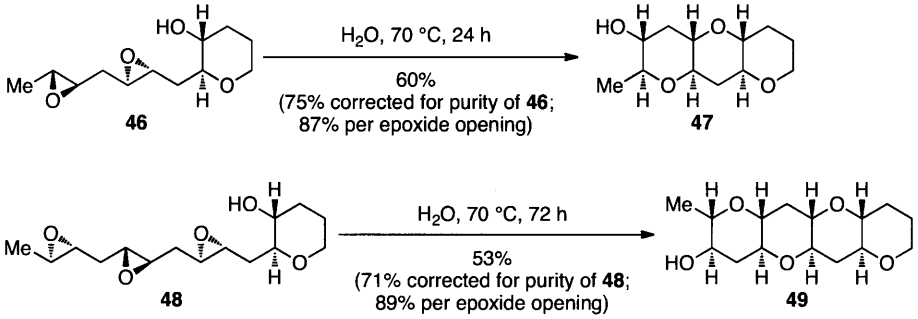
14 **44** 86% **45** 14%

Dr. Vilotijevic demonstrated that *endo*-selective cyclization promoted by water is extensible to cascades of two and even three epoxide openings, in emulation of the proposed biosynthesis of the ladder polyethers (Scheme 8).[44] In a single operation, the cascade reactions of **46** and **48** generate THP triad **47** and tetrad **49**, which now represent significant subunits of the natural products. Despite extended heating in water, epoxide hydrolysis is limited, and the yields of **47** and **49** are quite good; better, in fact, than

[45] See Chapter II for further discussion of the pH dependence of regioselectivity in cyclizations of **41**.
[46] Wang, Z.; Cui, T.-Y.; Xu, Z.-B.; Qu, J. *J. Org. Chem.* **2008**, *73*, 2270.

yields in comparable cascades of two or three epoxide openings promoted by strong acid or strong base,[34b,36,37b,c] a testament to the mildness of water as activator.

Scheme 8. *Endo*-selective cascade reactions promoted by neutral water (Vilotijevic and Jamison, ref 44).



Dr. Jeffery A. Byers in our group has studied the mechanism of the water-promoted cyclization of THP-templated epoxy alcohol **41**.[47] His results indicate that cyclization occurs in bulk solution rather than at an interface or in micelles. They also reveal that cyclization of **41** is under complete kinetic control; as expected, epoxide opening is irreversible. Kinetics data indicate that in the transition state to *endo* cyclization, multiple water molecules are involved in activating **41**, presumably through an extended network of hydrogen bonds. Thus water is distinctly *not* acting a simple mild Brønsted acid. Instead, it appears to serve as a dual, bifunctional catalyst that activates both epoxide electrophile and alcohol nucleophile. Water is a unique solvent for organic reactions: its ability to "delocalize" protons greatly facilitates proton transfer and makes concomitant activation of epoxide and hydroxyl feasible.[48]

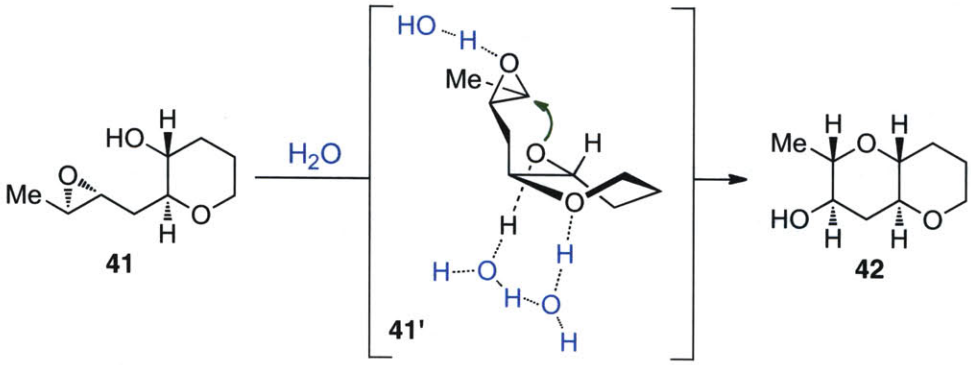
The ring oxygen of the THP template of **41** is required for *endo* selectivity; as a good hydrogen bond acceptor, it is proposed to anchor the network of hydrogen bonds and stabilize the conformer of the epoxy alcohol that leads to *endo* cyclization. Dr. Byers proposed particular twist boat **41'** as a conceivable reactive conformer (Figure 2). A twist boat conformation is attractive, as it perturbs the trajectory of approach of the hydroxyl

[47] J. A. Byers and T. F. Jamison, *J. Am. Chem. Soc.*, **2009**, *131*, 6383.

[48] (a) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302. (b) Bonollo, S.; Lanari, D.; Vaccaro, L. *Eur. J. Org. Chem.* **2011**, *in press*. [DOI: 10.1002/ejoc.201001693] (c) Sharp, K. A.; Vanderkooi, J. M. *Acc. Chem. Res.* **2011**, *43*, 231. (d) Ball, P. *Chem. Rev.* **2008**, *108*, 74. (e) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.

group to the epoxide. Such perturbation could be critical, as theoretical studies from Houk[49] and Coxon[50] and experimental evidence from Stork[31] suggest that the geometry of nucleophilic approach dictates the regioselectivity of epoxide opening.

Figure 2. Plausible twist boat conformer **41'** en route to *endo* cyclization (Byers and Jamison, ref 47).



Thus we propose that the templating effect of the THP ring of **41** stems from its ability to anchor a network of water molecules that both activates the substrate and constrains it in an unusual conformation, which perturbs the alcohol's angle of attack. This anchoring effect is most important. However, the ring oxygen may also serve as an inductive electron-withdrawing group. If there is some zwitterionic character in the transition states to cyclization (*i.e.*, a partial positive charge on the epoxide), then its electron-withdrawing effect may discourage the development of positive charge at the nearby *exo* site and consequently discourage attack at this site.[51]

F. Brief outline of work presented in this thesis.

We present herein an account of four closely aligned projects (Figure 3). All of these concern the development and examination of *endo*-selective epoxide-opening cascades promoted by water, as a means to generate ladder polyether structures.

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[49] Na, J.; Houk, K. N.; Shevlin, C. G.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 8453.
[50] Coxon, J. M.; Thorpe, A. J. *J. Org. Chem.* **1999**, *64*, 5530.
[51] See Chapter II for evidence zwitterionic character in the transition states to *endo* and *exo* epoxy alcohol cyclization under activation by neutral water.

- Chapter II recounts the investigation of water-promoted cyclization of trisubstituted epoxides.
- Chapter III contains detailed kinetic analysis of a cascade reaction in water and concludes with a proposed stepwise mechanism for these processes.
- Chapter IV presents preliminary results concerning a versatile 1,3-dioxane template for *endo*-selective epoxide opening.
- Finally, Chapter V describes the synthesis of the *FGH* ring system of the ladder polyether gambierol via an *endo*-selective epoxide-opening cascade promoted by water.

Throughout this work we have been guided and inspired by the striking cascades that conclude the postulated biosynthesis of the ladder polyethers.

Chapter II

Water-Promoted Epoxide Opening Accommodates Methyl Substitution.

A. The "problem" of methyl substitution in the biosynthesis of the ladder polyethers.

As was mentioned in Chapter I, methyl (Me) groups are the only substituents other than hydrogen found at ladder polyether ring junctions. Indeed, at least one Me-substituted ring junction is found in every member of this large family of natural products, from the most compact examples, hemibrevetoxin and brevenal,[1] to the recently isolated brevisin[2] and tamulamides.[3] Approximately one quarter of ring junctions across the entire set of structures are methylated (see Chapter I, Figure 1), and some ladder polyethers are more densely substituted. For example, brevetoxin B (**1**) bears Me substituents at five of its ten ring junctions (Scheme 1).

In the proposed biosynthesis of the ladder polyethers via *endo* epoxide-opening cyclization, the axial Me groups are proposed to arise from Me substituents that decorate certain epoxides in the polyepoxide cascade substrates.[4] For instance, five methylated epoxides are present in all (*R*,*R*)-polyepoxide **2**, Nakanishi's hypothesized precursor to brevetoxin B.[4a] There is some disagreement in the literature over whether **2** or all (*S*,*S*)-polyepoxide **3** is the more likely polyepoxide precursor to brevetoxin B; some contend[4b,c] that an activated carboxylate species is more likely to serve as the terminal electrophile of the cascade, as in the reaction of **3** (path b), than as terminal nucleophile, as in the reaction of **2** (path a).

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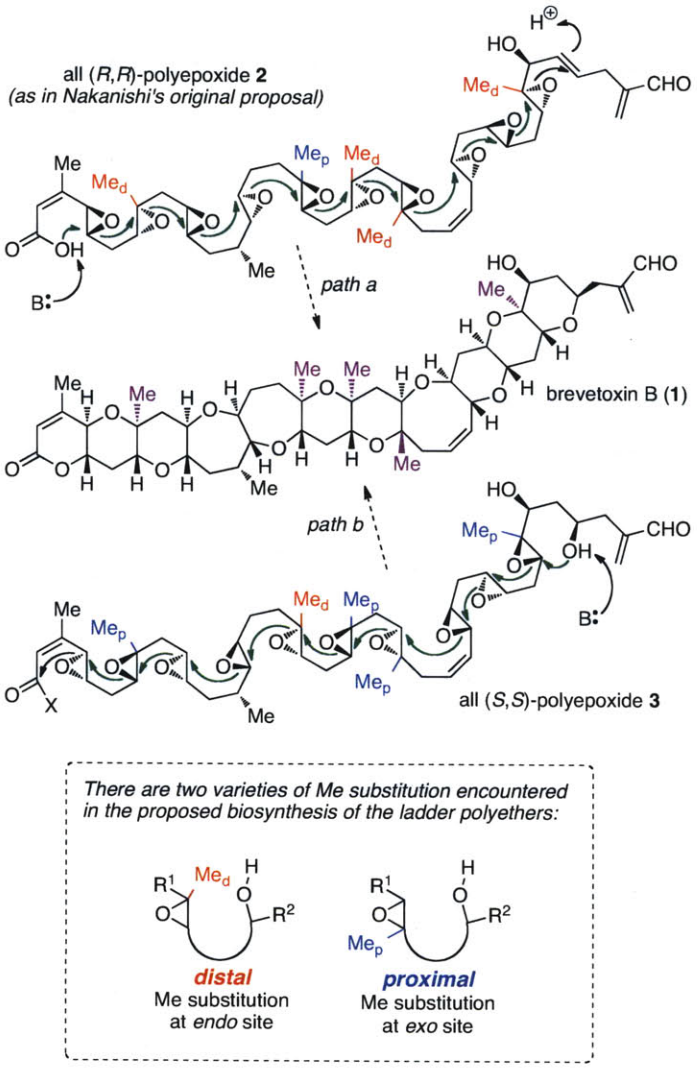
[1] Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7182.
[2] Satake, M.; Campbell, A.; Van Wagoner, R. M.; Bourdelais, A. J.; Jacocks, H.; Baden, D. G.; Wright, J. L. C. *J. Org. Chem.* **2009**, *74*, 989.
[3] Truxal, L. T.; Bourdelais, A. J.; Jacocks, H.; Abraham, W. M.; Baden, D. G. *J. Nat. Prod.* **2010**, *73*, 536.
[4] (a) Lee, M. S.; Qin, G.-w.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234. (b) Nicolaou, K. C. *Angew. Chem. Int Ed. Engl.* **1996**, *35*, 588. (c) Gallimore, A. R.; Spencer, J. B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4406.

Scheme 1. Two proposed biosyntheses of brevetoxin B.



Nature has conceived two very distinct varieties of Me substitution in these polyepoxide substrates. The Me groups that adorn the trisubstituted epoxides of **2** and **3** are encountered both *distal* (Me_d, shown in red, Scheme 1) and *proximal* (Me_p, shown in blue) to the internal nucleophile. Throughout this document we will refer to *distal* Me groups as those sited at the *far* side of the epoxide with respect to that pendent nucleophile, while *proximal* Me substituents are those placed at the *near* side of the epoxide (see inset, Scheme 1).

A mixture of distal and proximal epoxides is encountered in both **2** and **3** (Scheme 1). Thus, regardless of which direction the epoxide-opening cascade proceeds, both varieties of epoxide substitution will be incorporated in the cascade. This is true not only

for the proposed biogenesis of brevetoxin B but indeed for nearly all ladder polyethers bearing more than one axial methyl group, including brevetoxin A, maitotoxin, gambierol, gambieric acid, yessotoxin, and gymnocin B. All of these natural products are proposed to arise from polyepoxides that contain "out-of-register" mixtures of both distally and proximally substituted epoxides.[5]

This point is critical, as the Me group can exert a rather powerful directing effect on the regioselectivity of epoxide opening, especially upon activation with acid to generate epoxonium intermediates. The McDonald group, in particular, has extensively studied *endo*-selective epoxide-opening cascades promoted by acid and directed by distal Me substituents.[6] These methods have been applied to the total synthesis of fused polyether natural products.[7] Distal Me groups have also been used as directors in *endo*-selective cyclization methods developed by Morimoto[8] and Floreancig,[9] methods which likewise involve the generation of epoxonium intermediates. The success of all these methods hinges on the ability of an alkyl substituent to stabilize an α carbocation; the distal Me groups encourage the development of positive charge at the *endo* rather than *exo* site of attack in epoxonium intermediates, thereby promoting *endo* opening (Scheme 2, equation 1). McDonald[6e] and Floreancig[9] have shown that *trans*-disubstituted epoxides lacking these directors can be incorporated into cascades of epoxonium openings, at least in the context of oxepane formation, but *endo* selectivity suffers (equations 2 and 3).

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[5] To the best of our knowledge, the only exceptions to this "out-of-register" rule are the ciguatoxins, gymnocin A, and tamulamide A. The ciguatoxins, a set of closely related structures, all contain only a single axial Me group. Gymnocin A and tamulamide A both bear two axial Me groups. The pair of Me groups in both natural products are "in register," meaning that the proposed substrates for an epoxide-opening cascade contain either two distal or two proximal epoxides.

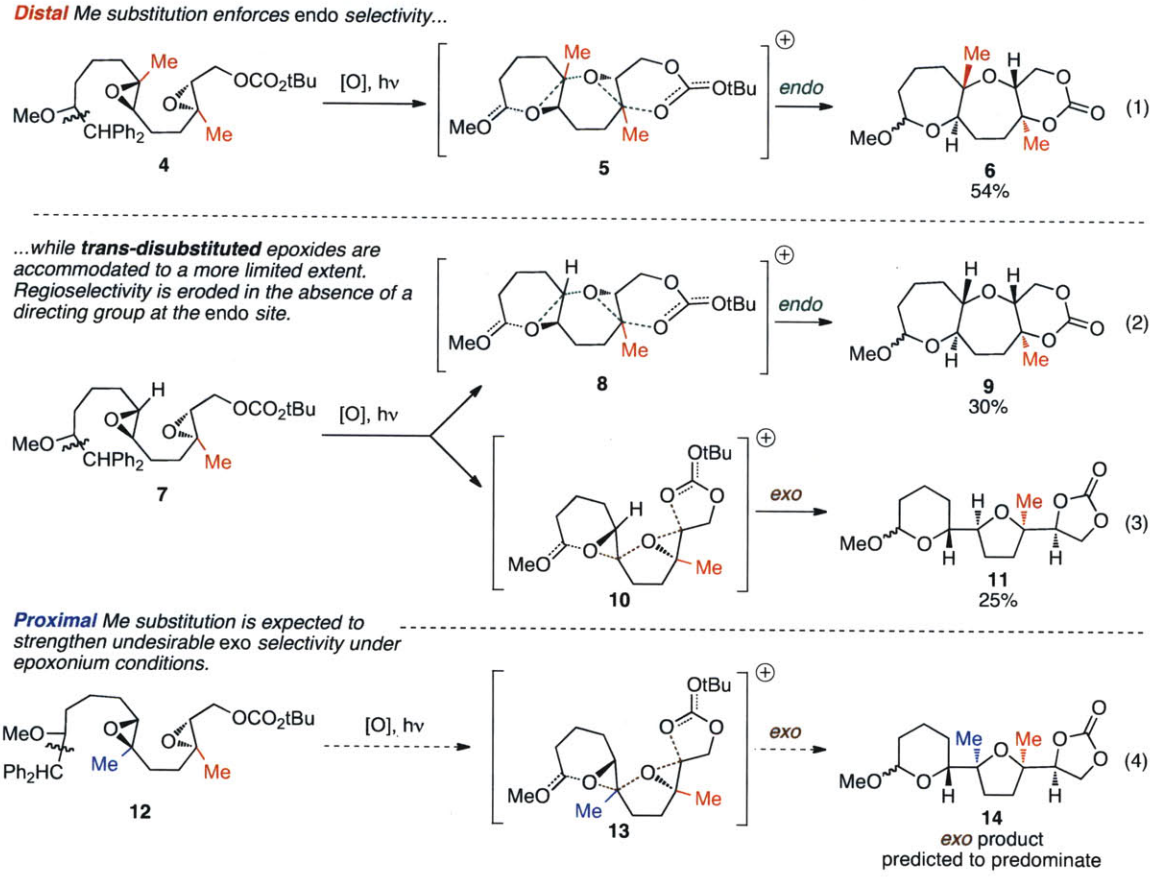
[6] *original reports:* (a) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917. (b) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodriguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515. (c) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2003**, *5*, 2123. (d) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *Org. Lett.* **2004**, *6*, 4487. (e) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586. (f) Tong, R.; McDonald, F. E.; Fang, X.; Hardcastle, K. I. *Synthesis* **2007**, *15*, 2337. *accounts:* (g) Valentine, J. C.; McDonald, F. E. *Synlett* **2006**, *12*, 1816. (h) McDonald, F. E.; Tong, R.; Valentine, J. C.; Bravo, F. *Pure Appl. Chem.* **2007**, *79*, 281.

[7] (a) Tong, R.; Valentine, J. C.; McDonald, F. E.; Cao, R.; Fang, X.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2007**, *129*, 1050. (b) Tong, R.; McDonald, F. E. *Angew. Chem. Int. Ed.* **2008**, *47*, 4377. (c) Boone, M. A.; Tong, R.; McDonald, F. E.; Lense, S.; Cao, R.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2010**, *132*, 5300.

[8] Morimoto, Y.; Yata, H.; Nishikawa, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 6481.

[9] Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915.

Scheme 2. Opening of distal, proximal, and *trans*-disubstituted epoxides under epoxonium conditions (equations 1-3 taken from Floreancig and Houk, ref. 9).



One would logically expect that acidic activation of proximally substituted epoxides should only amplify the intrinsic, undesirable *exo* selectivity, as the directing Me group will now stabilize charge at the *exo* site of attack. Indeed, in his synthesis of glabrescol, Corey documented exceptionally high *exo* selectivity in a cascade involving cyclizations of proximally Me substituted epoxides.[10] Diepoxide **12**, which comprises both proximally and distally substituted epoxides, should by literature precedent and by analogy with the reaction of **9** cyclize primarily to the *exo* product (Scheme 2, equation 4). In fact, when we began our work, there were no examples of the *endo*-selective opening of epoxides with proximal Me or other simple alkyl substituents, except for a

[10] Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328.

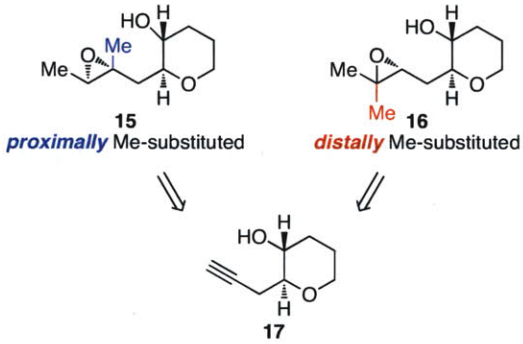
few cases of enzymatic catalysis[11] and one instance featuring a stronger (alkenyl) electronic directing group at the *endo* site of attack.[12]

If brevetoxin B and other ladder polyethers are indeed derived from cascades of *endo* epoxide openings, then any conditions nature employs in the biosynthesis must accommodate all three types of epoxide substitution. We began our project with the ambition that cyclization templated by a preformed tetrahydropyran (THP) ring and promoted by neutral water would be extensible to trisubstituted epoxides and that water would provide the first general solution to *endo*-selective epoxide opening. In particular, we surmised that promotion by neutral water was more likely to tolerate the challenging proximal substitution pattern than the acidic activation conditions prevalent in the literature. We hypothesized that by avoiding the generation of epoxonium intermediates, the electronic directing effect of a proximal Me group should be blunted.

B. Design and synthesis of trisubstituted monoepoxy alcohol model systems.

We began our investigation with the preparation of two simple THP-templated epoxy alcohols, proximally substituted **15** and distally substituted **16** (Scheme 3). Both of these cyclization substrates were derived from common intermediate **17**, a versatile terminal alkyne.

Scheme 3. Me-substituted epoxy alcohols **15** and **16**.



[11] (a) Shichijo, Y.; Migita, A.; Oguri, H.; Watanabe, M.; Tokiwano, T.; Watanabe, K.; Oikawa, H. *J. Am. Chem. Soc.* **2008**, *130*, 12230. (b) Matsuura, Y.; Shichijo, Y.; Minami, A.; Oguri, H.; Watanabe, M.; Tokiwano, T.; Watanabe, K.; Oikawa, H. *Org. Lett.* **2010**, *12*, 2226.
[12] Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545.

Alkyne **17** was initially prepared in our group by Dr. Timothy Heffron for the synthesis of trimethylsilyl-substituted epoxides.[13] This synthesis generates **17** in seven linear steps from the commercial, but costly, 5-trimethylsilyl-4-pentyn-1-ol. We resolved to develop a higher-throughput and lower-cost preparation of **17** and ultimately designed a five-step route (Scheme 4). We emphasize, however, that this procedure is ultimately much lower-yielding than that of Heffron and Jamison[13a] (6% over five steps vs. 36% over seven steps).

Synthesis of alkyne **17** began from inexpensive dihydropyran (**18**, Scheme 4). Deprotonation with nBuLi in TMEDA and capture of the anion with paraformaldehyde afforded allylic alcohol **19**.[14] Alkene **19** was then subjected to hydroboration with BH_3•SMe_2 and oxidized to furnish the 1,3-diol. We found that this polar intermediate was extremely difficult to extract from aqueous solution, and so oxidation with trimethylamine *N*-oxide (TMANO)[15] under nearly anhydrous conditions was much preferable to the more common alkaline H_2O_2 workup. Selective tosylation of the primary alcohol then gave tosylate **20**.[16] Resolution of the racemic mixture using an AMANO lipase[17] provided acetate **21** in excellent enantiomeric excess. Lastly, the tosylate of **21** was displaced with lithium acetylide (and its acetate group cleaved concomitantly) to yield alkyne **17**. Crude **17** can also be directly subjected to silyl ether

---

[13] (a) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339. Compound **3** has also been prepared in racemic form by McDonald and in antipodal form by Nakata; see: (b) Bowman, J. L; McDonald, F. E. *J. Org. Chem.* **1998**, *63*, 3680. (c) Matsuo, G.; Hinou, H.; Koshino, H.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **2000**, *41*, 903. (d) Suzuki, K.; Nakata, T. *Org. Lett.* **2002**, *4*, 2739.

[14] The conditions used are slightly modified from those of Lebouc, Delauney, and Riobé: Lebouc, A.; Delauney, J.; Riobé, O. *Synthesis* **1979**, *8*, 610.

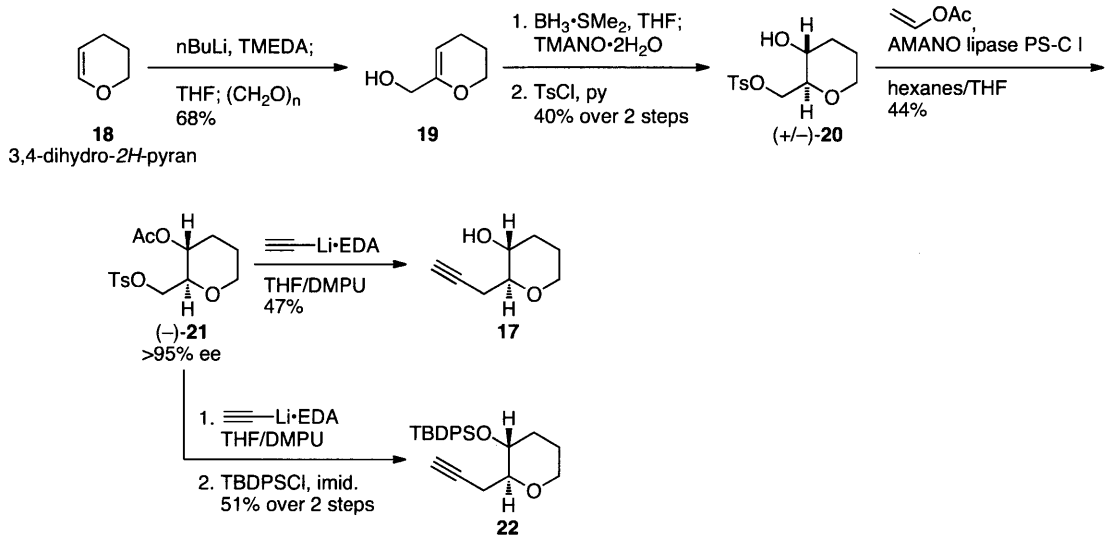
[15] *original reference:* Kabalka, G. W.; Hedgecock, H. C. *J. Org. Chem.* **1975**, *40*, 1776. *procedure taken from:* Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592.

[16] We previously reported the use of $TsCl/Et_3N/Me_3NHCl$ for this transformation (see: Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678.). However, we have since determined that chemoselectivity for the 1° over the 2° alcohol is lower under these conditions than with TsCl/pyridine. Yields are correspondingly lower with $TsCl/Et_3N/Me_3NHCl$, although reaction times are much improved. For more on the use of $TsCl/Et_3N/Me_3NHCl$ for tosylation, see: Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, *55*, 2183.

[17] For a procedure describing the use of this lipase in resolutions of 2° alcohols, please see: (a) Hong, B.-C.; Chen, Z.-Y.; Nagajaran, A.; Rudresha, K.; Chavan, V.; Chen, W.-H.; Jiang, Y.-F.; Zhang, S.-C.; Lee, G.-H.; Sarshar, S. *Tetrahedron Lett.* **2005**, *46*, 1281. For reviews of the use of lipases in organic synthesis, see: (b) Klibanov, A. M. *Nature* **2001**, *409*, 241. (c) Faber, K. *Biotransformations in Organic Chemistry*, 5th ed.; Springer-Verlag: Berlin, 2004; pp 94–123.

protection with TBDPSCl, to afford **22**.[18] This route has yielded multigram quantities of **17** and **22**.

Scheme 4. Synthesis of alkyne **17**.



With alkyne **17** in hand, we turned our attention first to proximally substituted epoxy alcohol **15**. As **15** is Me-substituted on both sides of the epoxide, we immediately envisioned its synthesis as arising from *syn*-1,2-difunctionalization of alkynes of the form of **17** or **22**. We initially attempted carbocupration[19] and Negishi carbometalation[20] to effect this transformation, but obtained only very low or no conversion. As substrate **17** is a bishomopropargylic alcohol, we then considered the possibility of a directed carbometalation.[21] Thompson's method for directed methylmetallation of alkynes with $TiCl_4$ and $AlMe_3$[22] obliged; methylmetallation of **17** and workup with iodine smoothly generated the alkenyl iodide, which was isolated as **23** after protection with triethylsilyl

[18] The two-step sequence from **21** to **22** provides the alkyne in slightly higher yield than isolation of **17** directly, as recovery of **17** from aqueous solution after extraction is challenging, due to the large quantity of DMPU present.

[19] *for methylcupration, see:* (a) Marfat, A.; McQuirk, P. R.; Helquist, P. *Tetrahedron Lett.* **1978**, *19*, 1363. *general overview:* (b) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

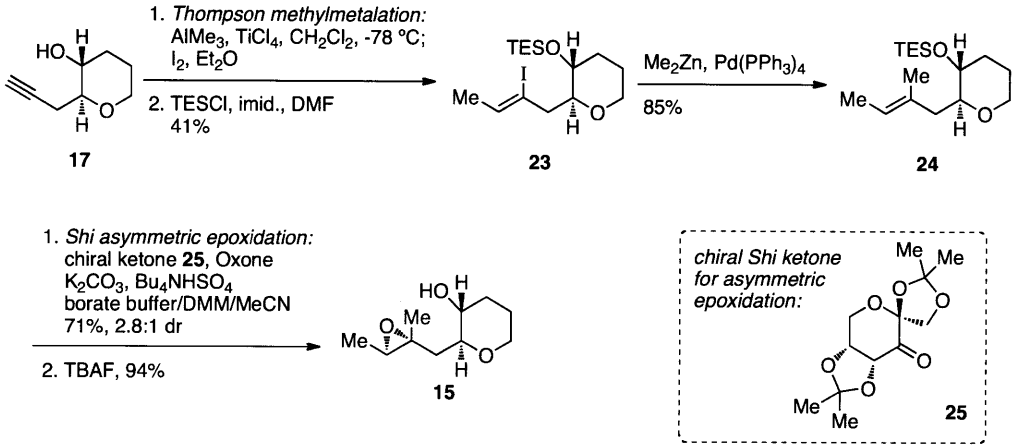
[20] *initial report:* (a) Van Horn, D. E.; Negishi, E.-I. *J. Am. Chem. Soc.* **1978**, *100*, 2252. *report of carbometalation in the presence of a free hydroxyl group:* (b) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E.-I. *J. Org. Chem.* **1981**, *46*, 4093. (c) *review:* Negishi, E.-I. *Dalton Trans.* **2005**, 827.

[21] Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

[22] (a) Schiavelli, M. D.; Plunkett, J. J.; Thompson, D. W. *J. Org. Chem.* **1981**, *46*, 807. (b) Ewing, J. C.; Ferguson, G. S.; Moore, D. W.; Shultz, F. W.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 2124.

chloride (TESCl, Scheme 5). The yield was modest, but **23** was obtained as a single stereo- and regioisomer.

Scheme 5. Synthesis of proximally substituted epoxy alcohol **15**.

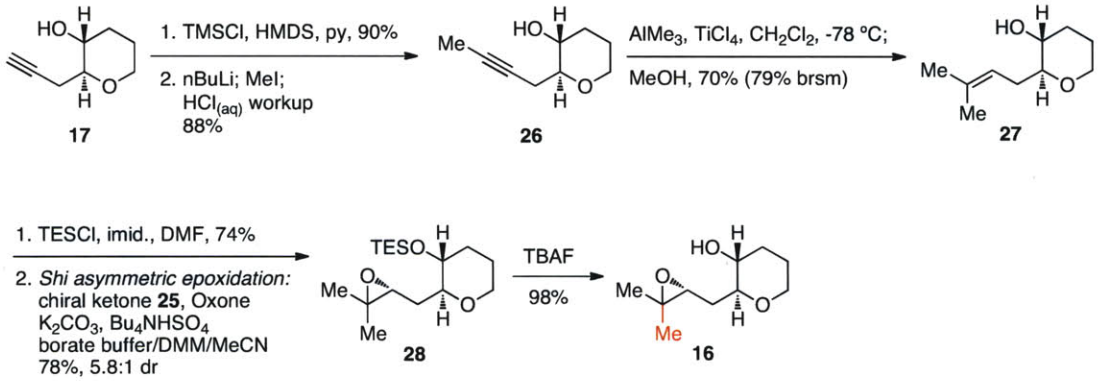


Alkenyl iodide **23** was methylated via Negishi coupling[23] with dimethylzinc to provide the trisubstituted alkene, which was then epoxidized under Shi's asymmetric epoxidation protocol.[24] Upon treatment with TBAF, the silyl ether was cleaved to provide epoxy alcohol **15**, the first substrate for cyclization studies.

To prepare distally substituted epoxide **16**, we again applied Thompson's methylmetalation (Scheme 6). Alcohol **17** was transiently protected as its TMS ether to enable selective methylation of the alkyne, furnishing **26**. Bishomopropargylic alcohol **26** proved an able substrate for methylmetalation, providing trisubstituted alkene **27** upon proton quench. As before, the alkene was obtained as a single regioisomer. After protection of the alcohol, this time as the TES ether, Shi asymmetric epoxidation afforded epoxide **28** in good diastereoselectivity. Finally, desilylation of **28** provided epoxy alcohol **16**.

[23] Negishi, E.-I.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71.
[24] (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.

Scheme 6. Synthesis of distally trisubstituted epoxy alcohol **2**.



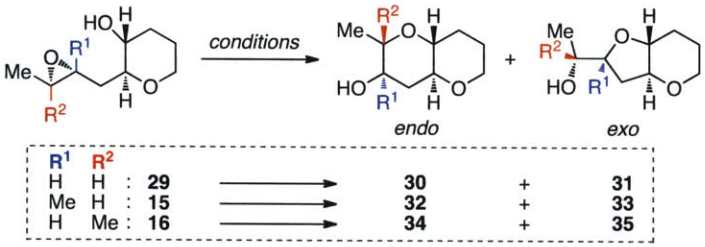
C. Cyclization studies of trisubstituted monoepoxy alcohols.

We began our experiments by cyclizing **15** and **16** under what has become a standard set of promoters within the Jamison group, Cs_2CO_3/MeOH, CSA, BF_3OEt_2, and deionized H_2O. These respectively exemplify activation by Brønsted base, Brønsted acid, Lewis acid, and, of course, neutral water.[25] For comparison's sake, we also cyclized the "original" THP-templated *trans*-disubstituted epoxy alcohol **29**, first examined by Dr. Ivan Vilotijevic in our group,[26] under the same conditions. Intriguingly, the three substrates, **15**, **16**, and **29**, showed widely divergent behavior under acidic and basic activation (Table 1).

[25] This particular group of acids and base was chosen because a survey of the literature indicated that each promoter was the most widely used example of each type. CSA is the Brønsted acid of choice for promoting cyclizations of vinyl-substituted epoxides, as pioneered by Nicolaou; see: (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. K.; Somers, P. K. *Chem. Commun.* **1985**, 1359. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. BF_3•OEt_2 is the Lewis acid promoter most commonly used by McDonald in his cascades of epoxonium openings, although his group has also used lanthanide triflates with good results (see ref. 6). Our group has also reported using BF_3•OEt_2 in cyclizations of TMS-susbtituted epoxides (see ref. 13a). Finally, Cs_2CO_3 was found to be the best basic promoter of cascades of TMS-substituted epoxides; see (c) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056. (d) Heffron, T. P.; Jamison, T. F. *Synlett* **2006**, 2329. (e) Heffron, T. P.; Simpson, G. L.; Merino, E.; Jamison, T. F. *J. Org. Chem.* **2010**, *75*, 2681.

[26] Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189.

Table 1. Dependence of regioselectivity on substitution and promotion in epoxide-opening cyclizations.



			***conditions and regioselectivity* (endo:exo):**[a]			
epoxy alcohol	R^1	R^2	Cs_2CO_3 (30 equiv) MeOH, rt	(+/-)-CSA (1 equiv) CH_2Cl_2, rt	$BF_3 \cdot OEt_2$ (25 mol%) CH_2Cl_2 -78 °C to rt	deionized H_2O rt
29	H	H	1 : 2.7	1 : 1.2	1.4 : 1	10 : 1
15	Me	H	3.0 : 1	1 : 5.2	1 : 11	4.9 : 1
16	H	Me	1 : 17	5.8 : 1[b]	>20 : 1[b]	>20 : 1

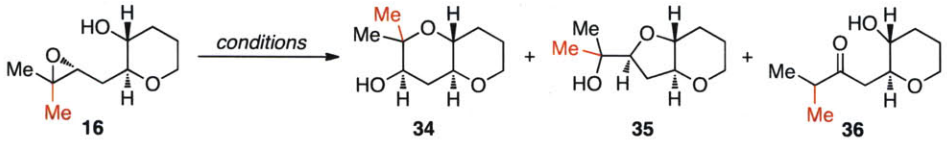
[a] Ratios determined by ^{1}H NMR spectroscopy. All reactions were carried out at 0.02 M and taken to >98% conversion of the epoxy alcohol. [b] Under these conditions, an isopropyl ketone side product was also formed; see Table 2.

As previously documented,[26] *trans*-disubstituted epoxide **29** cyclized with poor regioselectivity under both basic and acid promotion. Upon activation with Cs_2CO_3 in MeOH, **29** cyclized primarily to *exo* product **31**, a 6,5-fused bicycle. Acidic activation with both BF_3 and CSA afforded approximately 1:1 mixtures of *exo* product **31** and the desired *endo* product **30**, the THP diad. Neutral deionized water furnished **30** in 10:1 regioselectivity.

Proximally substituted epoxide **15** behaved differently. Consistent with expectation,[10] acidic activation afforded overwhelmingly the *exo* product, 6,5-fused **33**. However, we were pleased to see that **15** cyclizes with moderate selectivity for the desired *endo* product **32** in Cs_2CO_3/MeOH, with a measured regioselectivity of 3.0:1. We assume this selectivity arises from a steric preference, as the activated alkoxide nucleophile can more easily approach the 2° *endo* site as compared to the 3° *exo* site. More exciting was the discovery that neutral water promotes *endo*-selective cyclization of **15**, affording the desired THP diad **32** with nearly 5:1 regioselectivity. We believe that these two results together constitute the first examples of 6-*endo*-selective epoxide-opening cyclization of a proximally Me-substituted epoxide in the absence of either enzymatic control[11] or a more powerful directing group at the *endo* site.[12]

Consistent with literature precedent,[6,8,9] distally Me-substituted epoxy alcohol **16** cyclized with high *endo* selectivity under acidic promotion (Tables 1 and 2). Indeed, CSA was found to give nearly 6:1 *endo* selectivity, and upon cyclization with BF_3•OEt_2 at low temperature, no trace of *exo* product **35** could be detected. However, under acidic promotion, isopropyl ketone **36** was observed (Table 2, entries 1-3). This side product is proposed to arise via 1,2-hydride shift, a reaction pathway that was especially pronounced upon activation with BF_3•OEt_2 (entry 2). We must acknowledge that BF_3•OEt_2 has long been known to be an exceptionally efficient promoter of Wagner-Meerwein rearrangement of epoxides into ketones and aldehydes[27]; it is conceivable that another Lewis acid (e.g., a lanthanide triflate[6d,f]) could provide comparably high *endo* selectivity with less competing ketone formation. That said, we were again delighted to see that neutral water was a superb promoter for THP formation (Table 2, entry 4). Cyclization in water proceeded with >20:1 selectivity, comparable to that obtained with BF_3, but was not accompanied by ketone formation. Thus neutral water is an exceptionally mild and efficient promoter for *endo* cyclization of distally Me-substituted epoxide **16**.

Table 2. Cyclization of distally substituted **16** under acidic conditions and in neutral water. Formation of ketone **36**.



entry	conditions[a]	T (°C)	*t*	**34**:**35**:**36**[b]
1	(+/-)-CSA (1 equiv) CH_2Cl_2	rt	4 h	5.8 : 1 : 0.5
2	BF_3•OEt_2, (25 mol%) CH_2Cl_2	-78 to rt	30 min	2.2 : 0 : 1
3	0.1 M KP_i buffer, pH 1.8	rt	3 d	>20 : 1 : 1
4	0.1 M KP_i buffer, pH 7.0	rt	3 d	>20 : 1 : 0

[a] Reactions were carried out at 0.02 M and taken to >98% conversion of **16**.
[b] Determined by ^{1}H NMR.

[27] House, H. O.; Wasson, R. L. *J. Am. Chem. Soc.* **1957**, *79*, 1488.

For trisubstituted epoxides **15** and **16**, we also explored the relationship between regioselectivity of cyclization and the pH of the aqueous medium (Figure 1). For comparison, we overlay this data against that for *trans*-disubstituted **29**. In cyclizations of **29**, *endo* selectivity peaks at neutral pH and decreases precipitously as the aqueous reaction medium becomes either acidic or basic. Dr. Ivan Vilotijevic in our group was first to document this interesting phenomenon,[26] and Dr. Jeffery A. Byers has since made extensive investigation into why cyclization is much more selective in neutral water.[28]

We expected the same trend for trisubstituted **15** and **16**. However, *endo* selectivity in cyclizations of proximal **15** peaked not at neutral pH but in mildly basic solution, with the best regioselectivity (5:1 to 6:1) observed around pH 9.[29] *Endo* selectivity in cyclizations of **15** decreased dramatically on moving into acidic solution. Regioselectivity declined more gradually on shifting toward pH 12. Remarkably, distally substituted **16** cyclized with >20:1 *endo* selectivity at all pH between 2 and 8. Only at pH 10.5 and above did *exo* cyclization predominate for **16**. Thus there appeared to be an optimal range between pH 8 and 9 at which all three varieties of epoxide cyclize with good (≥5:1 or better) *endo* selectivity (Figure 1).

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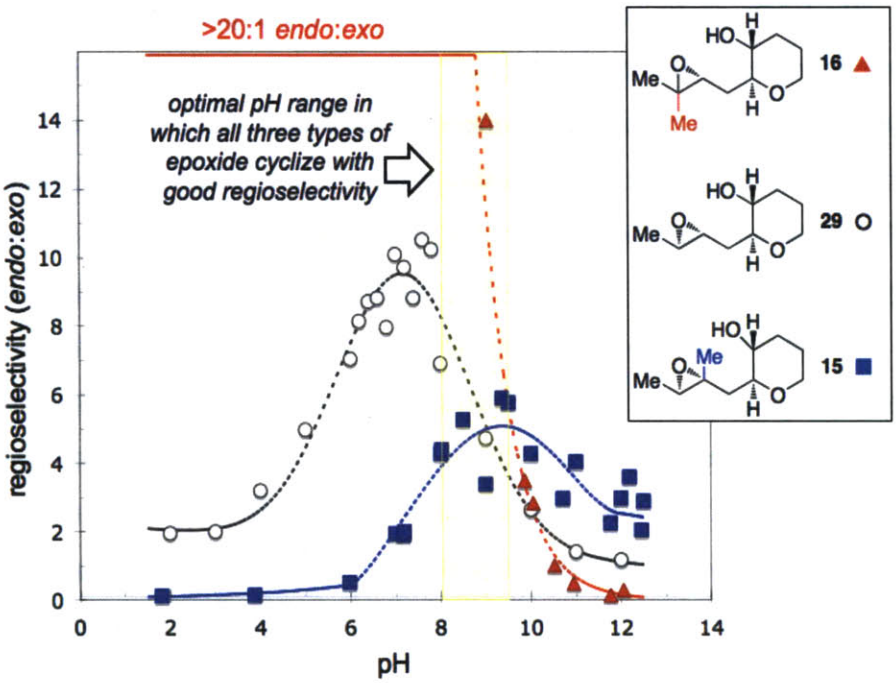
[28] (a) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383. (b) Jeffery A. Byers, Ivan Vilotijevic, and Timothy F. Jamison. *Manuscript in preparation.*

[29] The *endo*:*exo* selectivity of cyclization of **15** in 1 M potassium phosphate buffer at pH 7 was only 2:1, conspicuously lower than the 4.9:1 observed in unbuffered deionized water. This fact points to a non-innocent role for the potassium phosphate buffer; we surmise that some Lewis acid-promoted cyclization occurs in the presence of 1 M [K^+]. In cyclizations of **16** and **29**, regioselectivities were identical in reactions performed in pH 7 buffer and deionized water.

Figure 1. Dependence of regioselectivity on pH in epoxide-opening cyclizations. (All cyclizations carried out in 1.0 M potassium phosphate buffer at room temperature.)



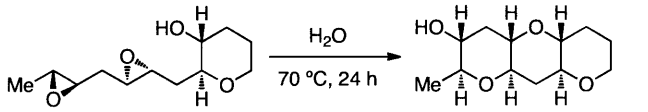
The primary lesson from study of epoxy alcohols **15**, **16**, and **29** was that water is a uniquely versatile promoter for *endo*-selective epoxide-opening cyclization. Of the four modes of activation examined, only neutral water induced *endo* opening of all three varieties of epoxide encountered in the biogenetic hypothesis: *trans*-disubstituted and proximally and distally trisubstituted. Unlike more traditional acidic and basic activators, water overcomes the steric and electronic directing effects of Me substituents. Furthermore, water was not only the most general but also the best promoter in each case, affording the highest *endo* selectivity and cleanest reaction (Table 1). Interestingly, *endo* selectivity was not uniformly high for the three epoxy alcohols. Proximally Me-substituted **15** cyclized in neutral water with the lowest *endo* selectivity (5:1), while distally Me-substituted **16** cyclized with the highest (>20:1). That is, the presence of Me directing group at the *exo* site of attack (as in **15**) does erode regioselectivity somewhat, while a Me group at *endo* site (as in **16**) reinforces it. While we reiterate that promotion by water is clearly distinct from simple acidic activation, this trend is consistent with

some development of positive charge on the epoxide in the transition states to cyclization.[28b] In other words, neutral water appears to induce zwitterionic transition states.

D. *Endo*-selective cascades incorporating trisubstituted epoxides. Part 1 — Preparation and study of the benchmark all-*trans*-disubstituted substrate.

These studies prompted a natural extension to cascade reactions that incorporate a mix of different substitution patterns. We were interested to test such reactions in neutral water or in the optimal range of pH described in Figure 1 above. Before initiating synthesis of a new set of cascade substrates, however, diepoxide **37** was prepared. Diepoxide **37** had already been synthesized and cyclized in water by Dr. Ivan Vilotijevic of our group (Scheme 7).[26] We resynthesized **37** in order to investigate its behavior under basic and acidic activation, as a point of comparison for the methylated substrates to come.

Scheme 7. Epoxide-opening cascade reaction of **37** promoted by water (Vilotijevic and Jamison, ref. 26).



37
4:1 overall dr

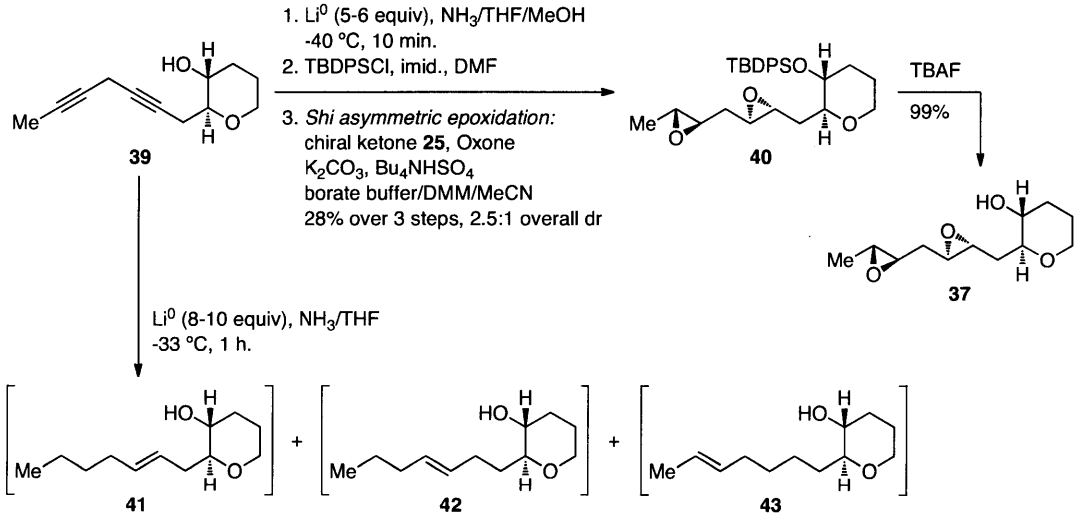
38
60%
(75% accounting for dr of **37**)

To prepare diepoxide **37**, we followed the basic synthetic strategy designed by Dr. Vilotijevic. However, for our work it was necessary to obtain **37** in high diastereomeric purity. As we intended to use Shi's asymmetric epoxidation protocol,[24] which in our hands typically affords between 5:1 and 10:1 enantio- or diastereoselectivity in each epoxidation, purification after epoxidation would be required. We therefore planned to install a UV-active silyl protecting group to enable preparative HPLC separation.

Our revised route to **37** is shown in Scheme 8. Synthesis commenced from diyne **39**, which was prepared by the previously reported procedure.[26] Dissolving metal reduction of **39** gave the *trans,trans*-skipped diene. If a large excess of Li metal (8 or

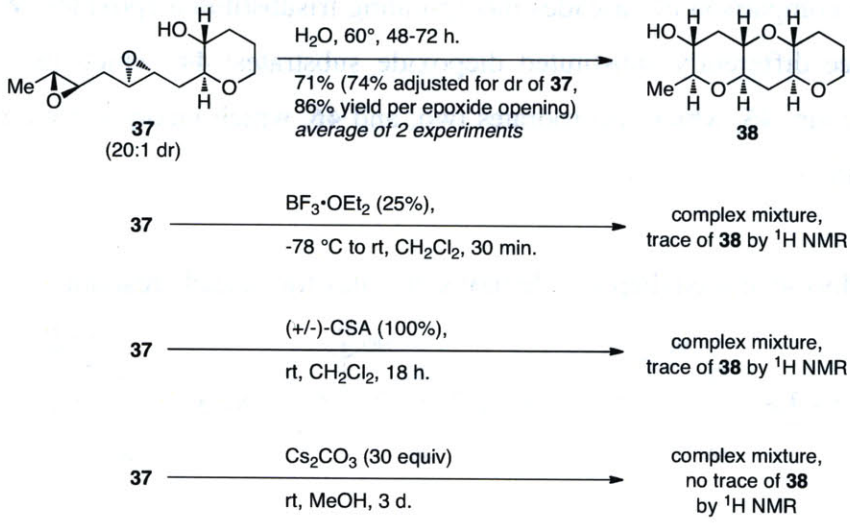
more mole equivalents) was used, the reaction was unreliable, sometimes affording none of the desired skipped diene product and instead providing three tentatively assigned side products **41-43** derived from over-reduction. These products presumably arise from base-induced isomerization of the desired skipped diene to conjugated dienes, which are subsequently reduced further. Reducing the quantity of Li^0 to 5-6 equiv improved yield and reproducibility, as did adding MeOH to neutralize strongly basic $LiNH_2$. Subsequent silyl protection of the alcohol and Shi asymmetric epoxidation of both alkenes provided diepoxide **40**, albeit in low 2.5:1 overall dr. Subsequent purification of **40** preparative HPLC afforded the compound in >20:1 dr. Lastly, desilylation gave diepoxy alcohol **37**.

Scheme 8. Synthesis of diepoxide **37**.



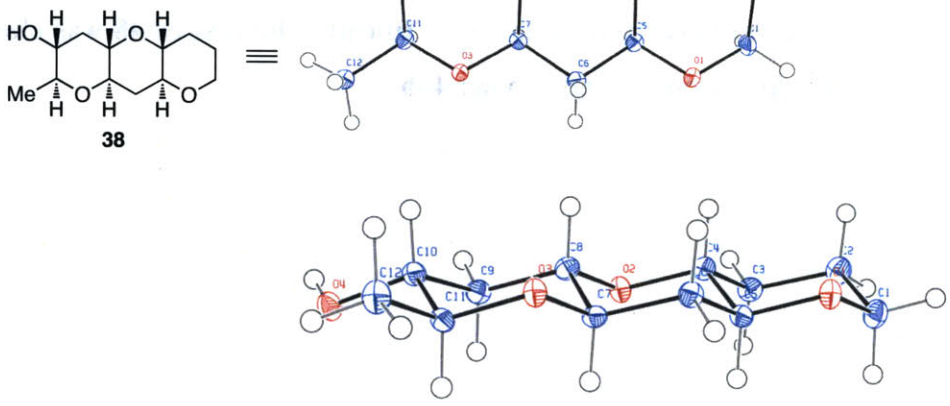
Isolated yields of THP triad **38** obtained from the cascade reactions of high purity **37** in deionized water were closely comparable to those determined by Dr. Vilotijevic[26] (Scheme 9). Our standard set of promoters, $BF_3{\bullet}OEt_2$ in CH_2Cl_2, CSA in CH_2Cl_2, and Cs_2CO_3 in MeOH, were also examined, but only the former two gave even a plausible trace of **38**.

Scheme 9. Cascades of diepoxy alcohol **37**.



In the course of these studies, a crystal structure of **38** was collected, which confirms its connectivity as well as the absolute and relative stereochemistry (Figure 2; see Experimental Section for details).

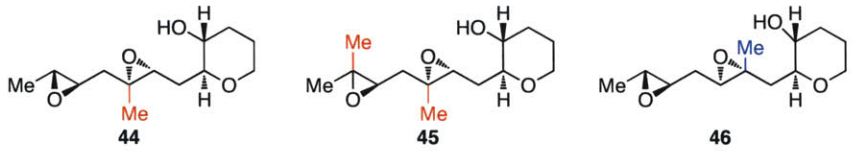
Figure 2. X-ray structure of THP triad **38**.



E. *Endo*-selective cascades incorporating trisubstituted epoxides. Part 2 — Synthesis of Me-substituted diepoxides.

The reactions of *trans*-disubstituted diepoxide **37** described above established a baseline for comparison of cascades incorporating trisubstituted epoxides. We decided to prepare three differently substituted diepoxide substrates: **44**, which incorporates one distal Me group; **45**, which incorporates two; and **46**, which incorporates a proximal Me group (Figure 3).

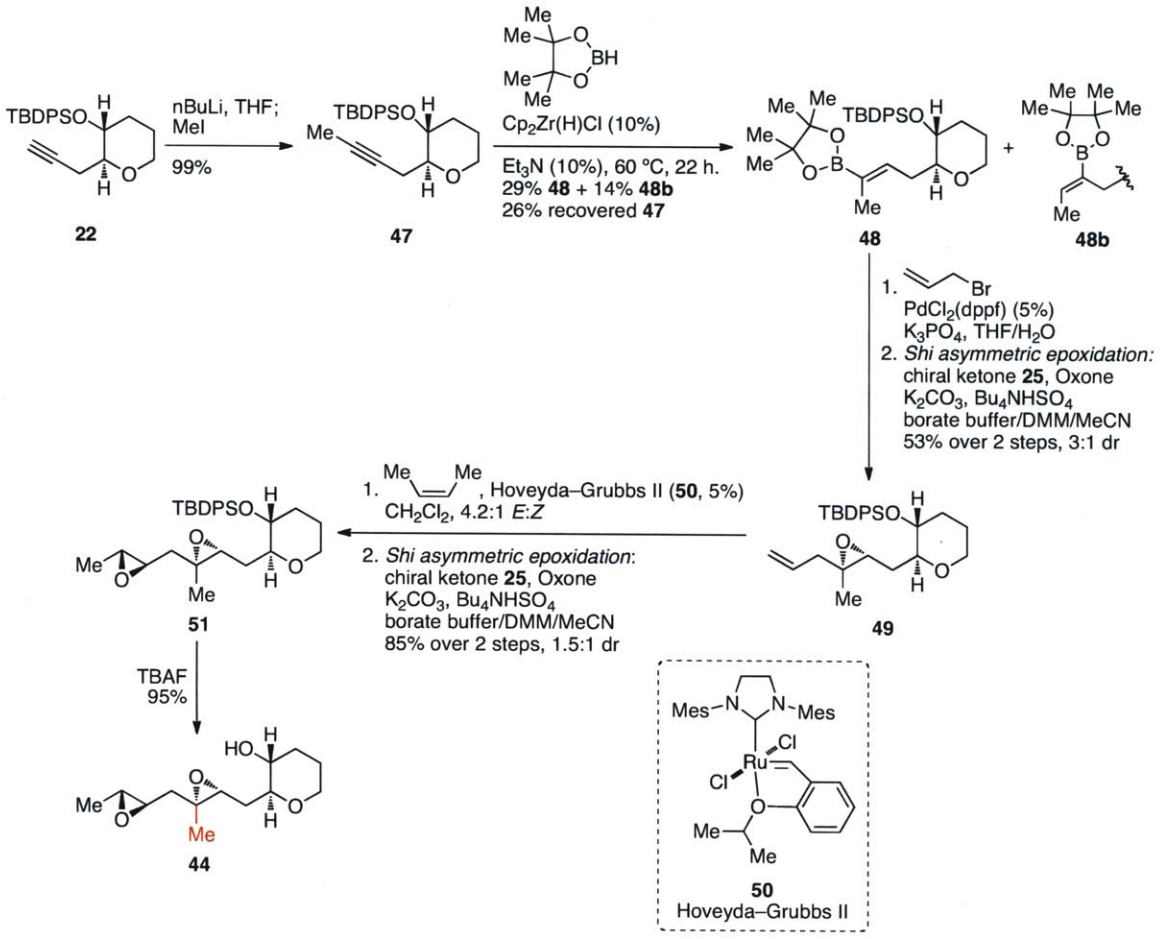
Figure 3. Me-substituted diepoxy alcohol substrates for cascade reactions.



Synthesis of all three compounds began from common intermediate **22**. Assembly of **44** was initiated with methylation of terminal alkyne **22** to internal **47** (Scheme 10). We then sought to perform regioselective hydrometallation of **47**. Uncatalyzed hydroboration of **47** proved impractically slow. Hydrozirconation of **47**, subsequent transmetallation to Zn, and quench with allyl electrophiles was possible, but such a protocol resulted in inseparable mixtures of regioisomers. We were pleased to find that Schwartz's reagent-catalyzed hydroboration with pinacolborane[30] afforded boronate ester **48** with respectable regioselectivity, albeit with poor conversion. The conditions described (60 °C, ~24 h) represent a compromise, as longer reaction times and higher temperatures led to lower mass recovery. Critically, the desired **48** was cleanly separable by chromatography from its regioisomer **48b**.

[30] (a) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127. (b) Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y. *Tetrahedron Lett.* **2005**, *46*, 8777.

Scheme 10. Synthesis of diepoxy alcohol **44**.



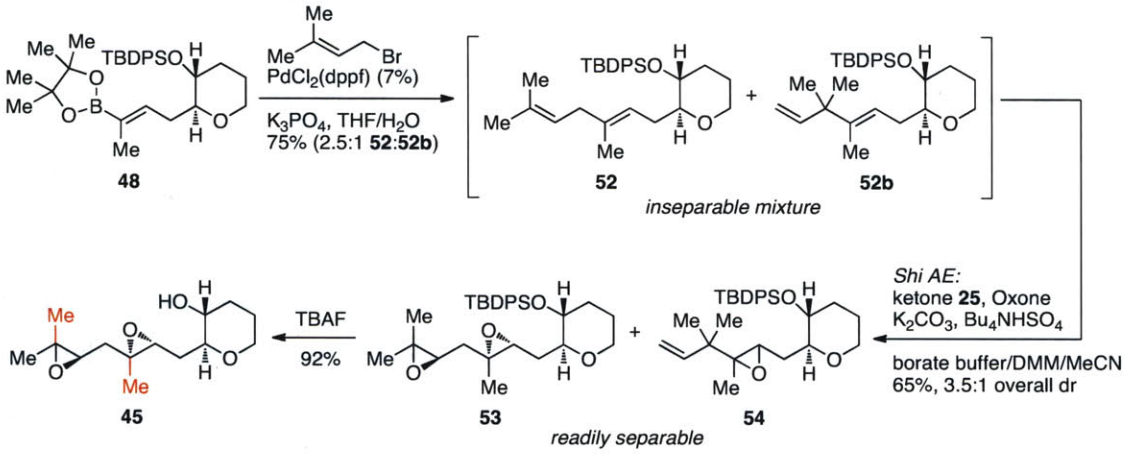
Alkenyl borane **48** was then cross-coupled with allyl bromide under conditions modified from those developed by Miyaura[31] to provide the skipped diene. In this cross coupling of **48**, the addition of at least stoichiometric quantities of water was found to be crucial to achieve activation of the boronate ester. Furthermore, dppf was superior to a number of other phosphines investigated, including SPhos, BINAP, and dppe. The crude skipped diene was carried into Shi epoxidation, an oxidation chemoselective for the more electron-rich trisubstituted olefin over the monosubstituted, which furnished epoxide **49**. Cross-metathesis[32] of **49** with *cis*-2-butene[33] catalyzed by Hoveyda–Grubbs 2nd

[31] Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Lett.* **1996**, *12*, 1117.
[32] (a) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58. (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (c) Connon, S. J.; Blecher, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.
[33] Patel, J.; Mujcinovic, S.; Jackson, W. R.; Robinson, A. J.; Serelis, A. K.; Such, C. *Green Chem.* **2006**, *8*, 450.

generation catalyst **50**[34] proceeded to the *trans*-disubstituted alkene in excellent yield and acceptable stereoselectivity. A second round of Shi epoxidation then provided diepoxide **51**. The unsatisfactory dr of **51** was improved to 8:1 to 10:1 by preparative HPLC, and desilylation then gave cascade substrate **44**.

Diepoxide **45** was synthesized by a slightly modified route (Scheme 11). From alkenyl boronate **48**, cross-coupling with prenyl bromide afforded a mixture of the desired skipped diene **52** and S_N2' product **52b**. These isomers were inseparable by column chromatography, but they were effectively resolved via Shi epoxidation. Only the more electron-rich trisubstituted alkene of **52b** oxidized, leading to monoepoxide **54**, while diene **52** was smoothly transformed to diepoxide **53**, which was easily purified. The overall dr of **53** was raised to 15:1 to 20:1 by preparative HPLC, and subsequent treatment with TBAF gave diepoxy alcohol **45**.

Scheme 11. Synthesis of diepoxy alcohol **45**.



The final Me-substituted diepoxide cascade substrate, **46**, was again prepared from common intermediate **22**. To begin, we first applied Kaneda's method for the Pd(II)-catalyzed haloallylation of alkynes,[35] which efficiently converted **22** to skipped diene **55** in excellent yield and with perfect stereo- and regioselectivity (Scheme 10). Addition of $NaHCO_3$ to the reaction neutralized traces of HBr and prevented desilylation.

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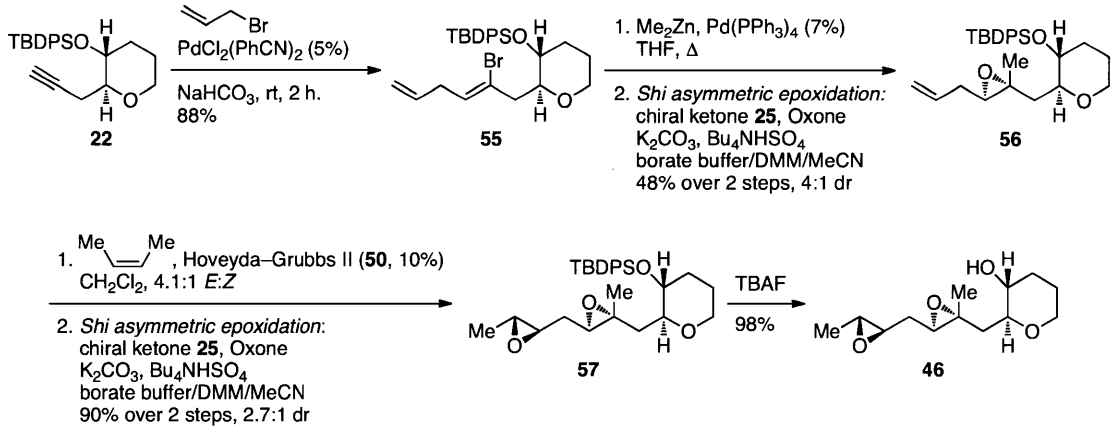
[34] Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
[35] (a) Kaneda, K.; Kawamoto, F.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *Tetrahedron Lett.* **1974**, *12*, 1067. (b) Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55.

We also explored chloro*crotyl*ation with 3-chloro-1-butene, but the reaction proceeded with unacceptably low regioselectivity. Alkenyl bromide **55** was methylated via Negishi coupling with dimethylzinc, and the resulting trisubstituted alkene was epoxidized using Shi's conditions to provide **56**. The terminal Me group was then installed through cross-metathesis with *cis*-butene, as in the synthesis of **44**. A second Shi epoxidation yielded diepoxide **57**, which was purified by preparative HPLC to afford a sample in 20:1 dr. Finally, treatment with TBAF furnished diepoxy alcohol **46**.

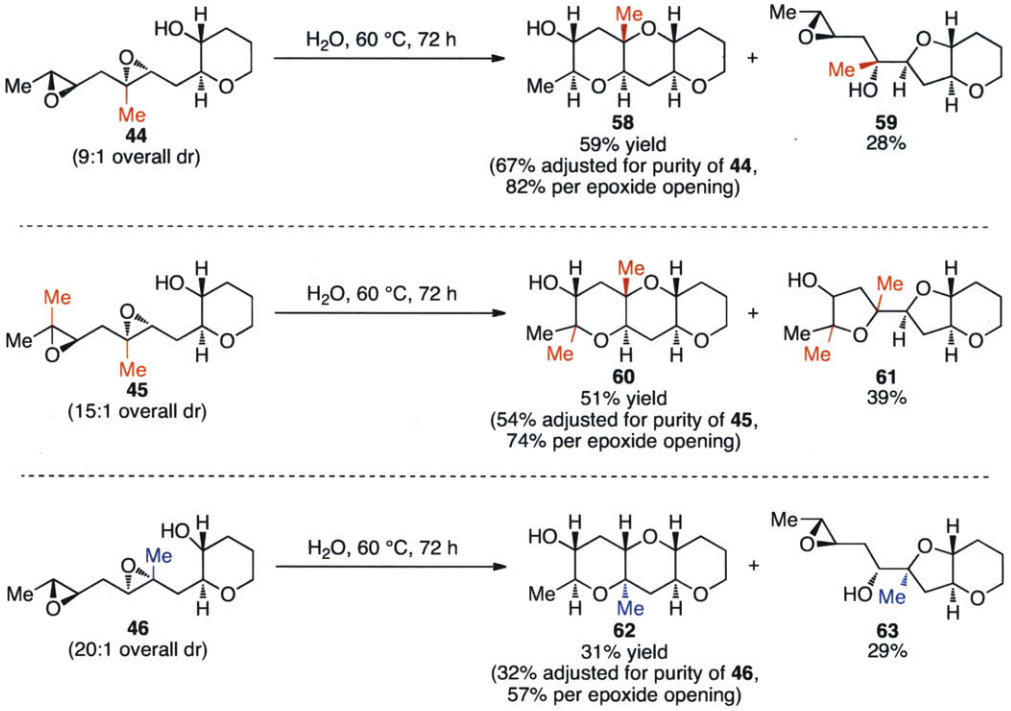
Scheme 12. Synthesis of diepoxy alcohol **46**.



F. *Endo*-selective cascades incorporating trisubstituted epoxides. Part 3 — Results of cascade reactions.

With Me-substituted diepoxy alcohols **44**, **45**, and **46** in hand, we investigated their behavior under our standard set of cyclization conditions. We present first the results of cyclization in neutral water (Scheme 13). In each case, the desired THP triad product is shown alongside the primary side product.

Scheme 13. Water-promoted *endo*-selective cascades of Me-substituted diepoxides. (Yields of THP triads **58**, **60**, and **62** are the average of at least two experiments.)



We were gratified to see that extended heating in deionized water successfully promoted the *endo* cyclization of all three substrates, transforming them to diversely methylated THP triads **58**, **60**, and **62** in modest to good yield. The cascade reaction of **46** was the lowest yielding of the three but perhaps the most notable, as to the best of our knowledge it represents the first example of an *endo*-selective epoxide-opening cascade accommodating a proximal Me substituent.

While water provided the desired THP triad in each case, yields were lower than we expected, based on the results from our monoepoxide model systems **15**, **16**, and **29**. Simple calculations on the basis of those models suggested that *trans*-disubstituted epoxides should cyclize with roughly 10:1 *endo* selectivity, or in about 91% yield per opening, proximal with roughly 5:1 *endo* selectivity and 83% yield, and distal with greater than 20:1 *endo* selectivity and 95% yield. However, overall yield, as calculated per epoxide opening, proved significantly lower in the cascade reactions of **44**, **45**, and **46**

(Scheme 13). Significant side product formation was detected, with compounds **59**, **61**, and **63** isolated and characterized.[36]

The relatively high yields of 6,5-fused bicycles **59** and **63** were surprising, as these two compounds appear to be the simple products of *exo* opening of the first epoxide by the templated alcohol. Nearly 30% of diepoxides **44** and **46** is funneled into these side products, which suggests that *endo* selectivity in the first epoxide opening is much lower than anticipated. That is, the implied regioselectivity is perhaps only 2:1 *endo*:*exo* in the first cyclization of distally substituted **44** and only about 1:1 in the first cyclization of proximally substituted **46** — again, much lower than the 20:1 and 5:1 regioselectivity, respectively, that was predicted by monoepoxy alcohols **15** and **16**. We later demonstrated that this effect is real and reproducible; the presence of a second epoxide further down the chain markedly reduces *endo* selectivity in the initial cyclization of a cascade. For further discussion of this phenomenon, see Chapter III.

The major side product from the reaction of doubly distally substituted **45** was different. THF **61** was formed in 39% yield. This compound could arise from a stepwise pathway in which 5-*exo* opening of the first epoxide is followed by 5-*endo* opening of the second, but we propose that a concerted pathway is also possible and perhaps more likely, by comparison with the results of the acid-promoted cascade reaction of **45** (*vide infra*). Scheme 14 presents this proposal (*endo*/*exo* pathway A). Protonation of the far epoxide of **45** by the trace of hydronium present in deionized water gives epoxonium **65**. The epoxonium of **65** then undergoes *endo* attack by the other epoxide, which can itself be opened *exo* by the templated alcohol to generate **61**. We hypothesize a concerted mechanism for this process rather than a stepwise one. Literature reports of electrophilic cascades of epoxonium openings are proposed to be concerted,[6,9] with specific computational support for this proposal provided by Houk and Floreancig.[9]

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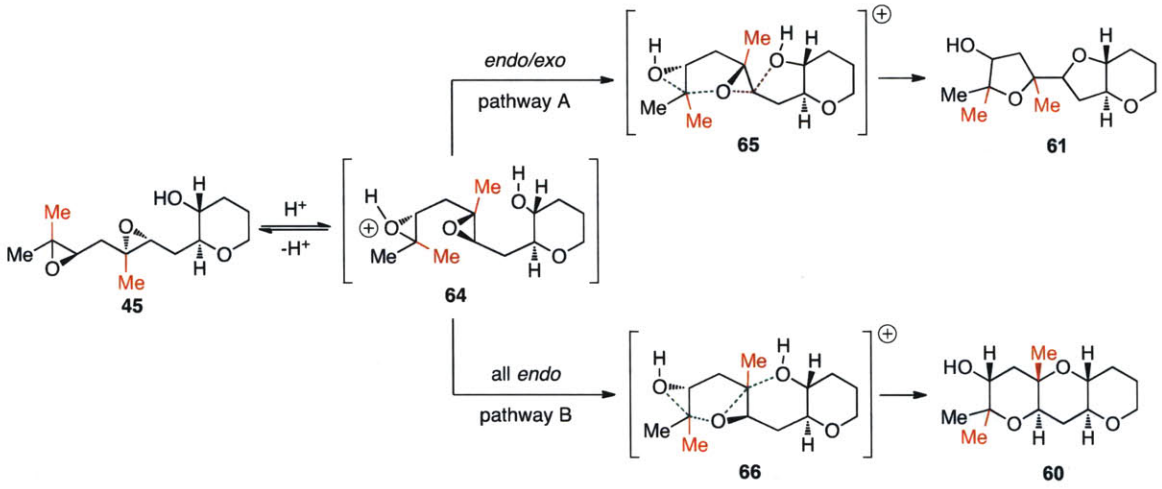
[36] In the reaction of each substrate (**44**, **45**, and **46**), additional side products were also observed but not characterized. For example, some highly polar products were detected, which constitute up to 10% of the mass balance. The compounds, invariably collected as mixtures of isomers, are presumed to be triols formed from epoxide hydrolysis.

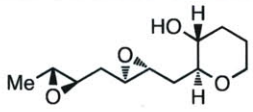
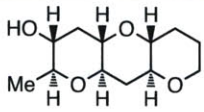
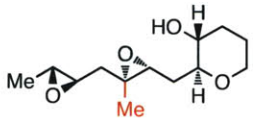
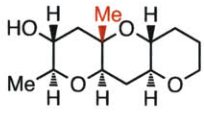
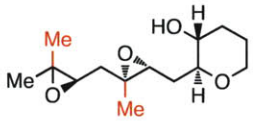
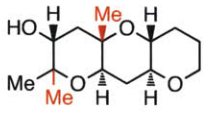
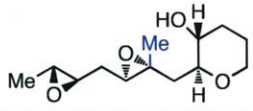
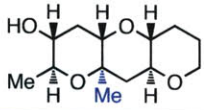
Scheme 14. Proposed acid-catalyzed pathways from diepoxide **45** to **60** and **61**.



Having raised the question of acid-catalyzed background reactions competing with the desired neutral water-promoted cascade, we must also introduce the possibility of an acid-catalyzed, electrophile-driven, concerted *endo*-selective cascade to the desired THP triad **60** (all *endo* pathway B, Scheme 14). It is conceivable that a substantial portion of **60** is formed through this manifold, even in neutral water, and not through the stepwise, nucleophile-driven cascade initiated from the templated alcohol. A portion of **44**, which bears just a single distal Me group, may also cyclize to THP triad **58** through the same mechanism. There is precedent from the McDonald group for THP formation in cascades of epoxonium opening.[6c]

Further corroboration of this hypothesized acid-promoted cascade mechanism came from the reaction of distally substituted diepoxides **44** and **45** under acidic conditions (Table 3). Activation of **44** and **45** with CSA and BF_3 induced cyclization to THP triads **58** and **60**, respectively, in yields comparable to those achieved in water.

Table 3. Cascades of Me-substituted diepoxides under various epoxide-opening conditions.

substrate		desired tris-THP product		*conditions and isolated yield[a] of desired product:* Cs_2CO_3 MeOH[b]	CSA CH_2Cl_2[c]	BF_3•OEt_2 CH_2Cl_2[d]	H_2O[e]
	**37**		**38**	0%	trace[f]	trace[f]	**74%**
	**44**		**58**	0%	46%	64%	**67%**
	**45**		**60**	0%	43%	61%	**54%** (+ 25% **61**)
	**46**		**62**	0%	0%	0%	**32%**

[a] Corrected for diastereomeric purity of starting material (between 7.5:1 and 20:1 for all cases, see Experimental Section); average of at least two experiments. [b] 30 equiv Cs_2CO_3, rt, 0.02 M. [c] 1 equiv (+/-)-CSA, rt, 0.02 M. [d] 0.25 equiv BF_3•OEt_2, -78 °C to rt, 0.02 M. [e] 60 °C, 0.02 M. [f] <5% (^{1}H NMR).

G. Unsuccessful cascade of three epoxide-opening cyclizations.

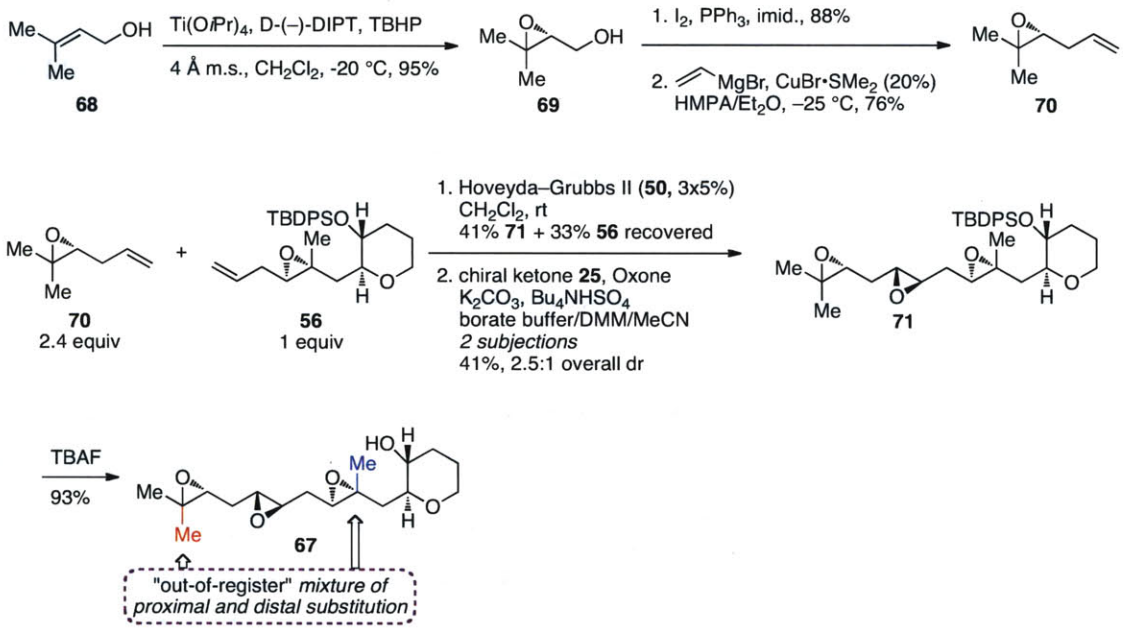
The reactions of diepoxide **44**, **45**, and **46** demonstrated that water accommodates all varieties of epoxide substitution encountered in the biosynthetic hypothesis. We then embarked on the logical next step: a more ambitious cascade of three epoxide openings. Specifically, we targeted **67** (Scheme 13), a cascade substrate incorporating all three varieties of epoxide (*trans*-disubstituted, proximally Me-substituted, and distally Me-substituted). Cascades of this triepoxide would be the first with an "out of register" mixture of proximal and distal substitution, as appear in the proposed biosyntheses of the brevetoxins and other ladders (see Scheme 1).

The synthesis of **67** began with epoxy alkene **56**, an earlier intermediate prepared in nine steps from dihydropyran (see Scheme 12). A second epoxy alkene (**70**) was generated in three steps from prenol, upon Sharpless asymmetric epoxidation,[37]

[37] *original references:* (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.;

iodination,[38] and displacement of the iodide with a vinyl metal reagent[39] (Scheme 15). Cross metathesis then joined **70** and **56** to provide the diepoxy alkene. This metathesis reaction suffered from low conversion of **56** and required repeated addition of several portions of catalyst. In retrospect, predimerization of **56** and **70** to the disubstituted alkenes might have improved yield.[32b] The alkene was converted to triepoxide **71** upon Shi epoxidation. This substrate proved sluggish, presumably because of the inductive electron-withdrawing effects of the surrounding epoxides, and required resubjection to the reaction conditions. Triepoxide **71** was formed in poor overall diastereopurity, but this was remedied by preparative HPLC to afford samples in 10:1 to 20:1 dr. Finally, desilylation of **71** gave **67**.

Scheme 15. Synthesis of triepoxide **67**.



Heating triepoxide **67** in deionized water led to the formation of two undesired triols: 6,5-fused **73** and 6,6-fused **74** (Scheme 16). Disappointingly, only a trace of the desired *endo* cyclization product, tetracycle **72**, was isolated, and the compound could not be purified completely. We attribute the formation of **73** and **74** to an acid-catalyzed

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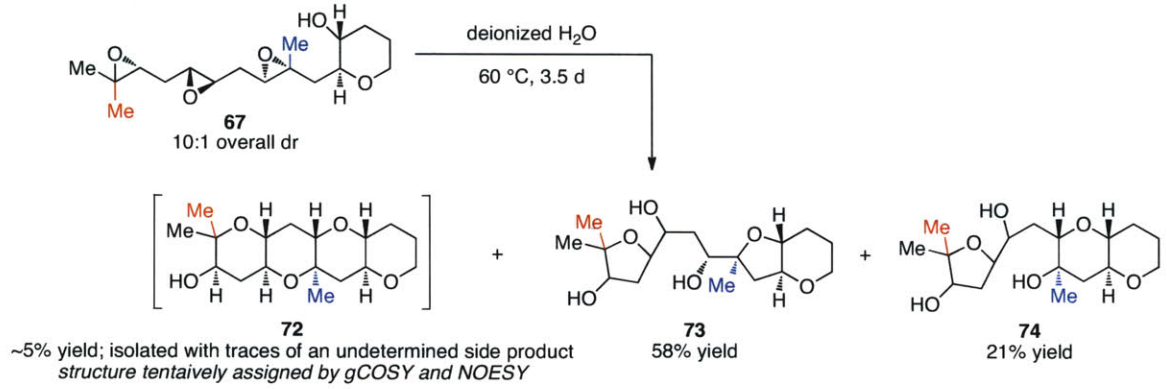
Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. *review:* (c) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

[38] Mori, K.; Brevet, J.-L. *Synthesis* **1991**, 1125.

[39] Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Tetrahedron Lett.* **1984**, *25*, 2069.

mechanism (Scheme 17). Protonation of the last epoxide of **67** would give epoxonium **75**. *Endo* attack of the central epoxide on epoxonium **75** (directed by the Me substituent) and hydrolysis then generates THF **76**. The surviving epoxide can then cyclize either *endo* or *exo*, to provide **74** and **73**, respectively. It is also possible that cyclization of the templated alcohol onto the first, proximally substituted epoxide could occur at the outset to give diepoxide intermediate **77** (Figure 4). The tertiary alcohol of **77** should presumably be poorly nucleophilic, making cyclization onto the central epoxide slow. Acid-promoted cyclization of the second and third epoxides would then have ample time to transpire instead.

Scheme 16. Reaction of triepoxide **67** in water.



Scheme 17. Proposed mechanism for formation of THF side products **73** and **74**.

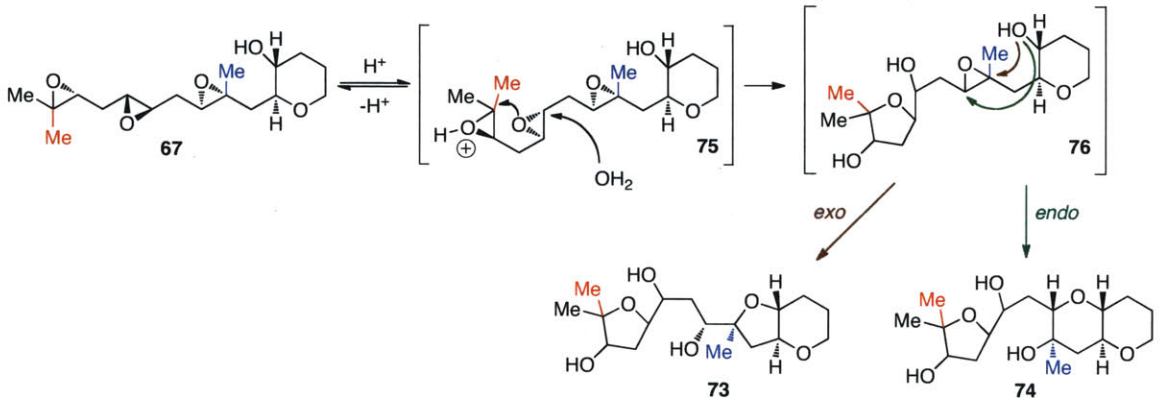
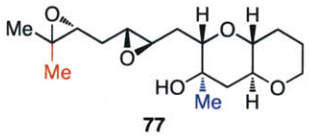


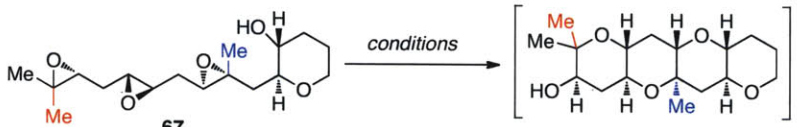
Figure 4. Potential intermediate **77**.



77

We attempted to limit epoxonium formation in the reaction of **67** by adjusting the reaction medium to a slightly basic pH. Potassium phosphate buffer at pH 8 or 9 was anticipated to provide an environment in which acidic activation was suppressed, while still remaining close enough to neutrality that cyclization promoted by neutral water rather than by hydroxide would predominate. Moreover, our earlier investigation of monoepoxides **15**, **16**, and **29** had also suggested that the range of pH between 7.5 and 9 was a good compromise for all three substitution patterns (see Figure 1). Indeed, at pH 8.2 and 8.5, slightly improved yields of tetracycle **72** were obtained, but these remained too low to be of synthetic utility (Table 4).

Table 4. Attempted optimization of the cascade reaction of **67**.



67
10:1 to 20:1 overall dr

72

entry	solvent[a]	T (°C)	*t*	yield **72**[b]
1	deionized H_2O	60	3.5 d	~5%
2	0.1 M KP_i buffer, pH 8.0	60	3.5 d	~5%
3	0.1 M $NH_3/(NH_4)_2SO_4$ buffer, pH 7.5	60	3.5 d	~3%
4	0.1 M $NH_3/(NH_4)_2SO_4$ buffer, pH 8.0	60	3.5 d	~4%
5	0.1 M $NH_3/(NH_4)_2SO_4$ buffer, pH 8.2	60	3.5 d	~9%
6	0.1 M $NH_3/(NH_4)_2SO_4$ buffer, pH 8.5	60	3.5 d	~8%
7	0.1 M $NH_3/(NH_4)_2SO_4$ buffer, pH 9.0	60	3.5 d	~6%
8	0.1 M $NH_3/(NH_4)_2SO_4$ buffer, pH 10.0	60	3.5 d	~3%

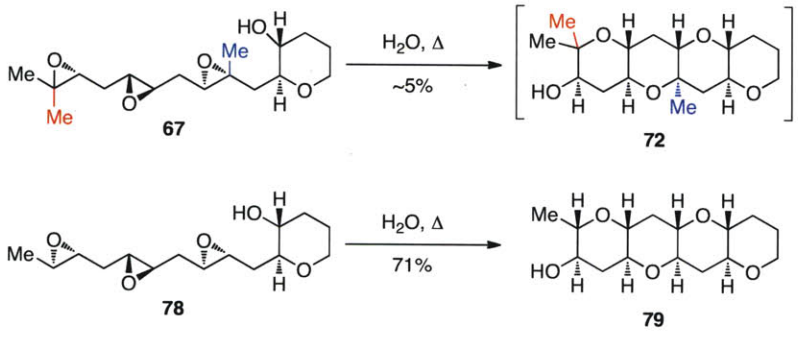
[a] All reactions were carried out at 0.02 M and taken to >98% conversion of **67**. [b] NMR yields.

Even in slightly basic solution, acid-catalyzed side reactions again outcompeted the desired stepwise pathway, and products **73** and **74** predominated. These results illuminate a major and general problem with water-promoted epoxide-opening cascades. As more epoxides are added to the chain, the number of potential unproductive side reactions among those epoxides increases, while the rate at which the desired stepwise

cascade propagates down the chain remains unchanged. Thus epoxides can cannibalize each other before the stepwise cascade reaches them. Extending water-promoted cascades to four or more epoxides is therefore likely to be difficult, at least in the absence of a tactic either to increase the rate of stepwise cyclization (perhaps through the use of a catalyst) or to suppress acidic activation of epoxides in the chain. Our group has had some success with the latter strategy; please see Chapter V for a discussion.

Lastly, we acknowledge that the yield of tetrad **72** obtained in the water-promoted reaction of **67** is far lower than the yield of its congener **79** formed in the corresponding reaction of all-*trans*-disubstituted triepoxide **78** (Scheme 18).[26] We again invoke the acid-catalyzed side reaction pathway shown in Scheme 17 and emphasize that polyepoxides incorporating trisubstituted epoxides are more delicate than those composed entirely of *trans*-disubstituted epoxides. We hypothesize that the additional Me substituent of the last epoxide of **67** makes its oxygen atom considerably more basic and therefore prone to protonation, which triggers destructive side reactions. Clearly, and despite our encouraging results with monoepoxides **15** and **16**, the incorporation of trisubstituted epoxides into cascades promoted by water remains a challenge.

Scheme 18. Comparison of cascade reactions of triepoxy alcohols. (Yield of **79** is calculated accounting for diastereopurity of **78** (Vilotijevic and Jamison, ref 26).)



To date, water remains the most versatile and broadly useful of the promoters we have found, and a small set of diversely Me-substituted fused THP tricycles can be assembled quickly and efficiently. Taken together, the foregoing explorations of water-promoted epoxide opening raised a few interesting questions about the mechanism of these reactions. It seems that efficient cascade reactions are less easily achieved than

monoepoxide cyclizations; cascades are more complicated than the sum of their parts. We became curious to probe the mechanism of cascades, as distinct from cyclizations of a single epoxide. Before we could improve our method, it seemed essential to delineate the competition between the desired stepwise cascade mechanism and acid-catalyzed side reactions. In our next project, we dissected a cascade reaction in detail (Chapter III).

H. Experimental Section

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Reactions were magnetically stirred unless otherwise stated. All temperatures are reported in °C.

Except where noted, dichloromethane was either distilled from calcium hydride or purified via an SG Water USA solvent column system. Except where noted, tetrahydrofuran (THF) and Et_2O were either distilled from a blue solution of benzophenone ketyl or purified via an SG Water USA solvent column system. Triethylamine was purified via an SG Water USA solvent column system. 1,3-Dimethyl-3,4,6,5-tetrahydro-2(1H)-pyrimidinone (DMPU) and tetramethylethylenediamine (TMEDA) were distilled from calcium hydride under argon. Reactions in water used deionized water without further purification. The pH of all aqueous buffers was checked within 24 hours of use.

Me_3N•HCl was placed under high vacuum for at least 15 minutes before use, to remove some water. Methyl iodide and allyl bromide were purified by filtration through basic alumina before use. Cs_2CO_3, NaI, and K_3PO_4 were oven-dried overnight before use. Chiral ketone **25**, used in Shi asymmetric epoxidation was prepared from D-fructose according to the procedure of Vidal-Ferran and coworkers.[40]

All other reagents and solvents were used as obtained, without further purification. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ceric ammonium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). Analytical HPLC was performed on the column phase indicated on a Hewlett-Packard 1100 Series HPLC. Preparative HPLC was performed on the column phase indicated on an Agilent 1200 Series HPLC.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Varian Inova-500 MHz spectrometer, a Bruker AVANCE-400 MHz spectrometer, or a Bruker AVANCE-600 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual $CHCl_3$ in $CDCl_3$ (7.27 ppm), C_6HD_5 in C_6H_6 (7.15 ppm), or CH_2Cl_2 in CD_2Cl_2 (5.32 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and app = apparent), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm), C_6D_6 (128.6 ppm), or CD_2Cl_2 (54.0 ppm) on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR. High Resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation

[40] Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143-10146.

Facility. Optical rotations were measured on a Jasco Model 1010 polarimeter at 589 nm. An X-ray structure of **38** was collected on a Siemens three-circle Platform Diffractometer coupled to a Bruker-APEX CCD detector at the MIT Department of Chemistry X-Ray Diffraction Facility.

General Procedures for Cascade Reactions of Diepoxy Alcohols 37, 44, 45, and 46.

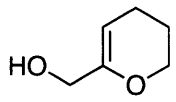
Representative procedure for reaction in **water**:
A sample of diepoxy alcohol was dissolved in deionized water to 0.02 M in a glass vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60 °C under air for 3 d. The solution was then cooled to rt and concentrated *in vacuo* (10 torr, 40 °C). The crude product mixture was chromatographed (30% EtOAc in hexanes or 50% EtOAc in hexanes, depending on product polarity, see individual procedures vide infra) to separate the desired tris-THP product (always the least polar and therefore the first off the column) from undesired cyclization products.

Representative procedure for reaction promoted by **Cs_2CO_3**:
A sample of diepoxy alcohol was dissolved in a solution of Cs_2CO_3 (30 equiv) in anhydrous MeOH to 0.02 M in a glass vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was stirred under air at rt for 3 d. The solution was then diluted with Et_2O, quenched with sat. NH_4Cl, and the aqueous layer was extracted with Et_2O. The combined organics were concentrated *in vacuo* without drying, and the crude product mixture was chromatographed (30% EtOAc in hexanes or 50% EtOAc in hexanes, depending on product polarity, see individual procedures vide infra) to separate the desired tris-THP product (always the least polar and therefore the first off the column) from undesired cyclization products.

Representative procedure for reaction promoted by **CSA**:
A sample of diepoxy alcohol was dissolved in CH_2Cl_2 to 0.02 M in an oven-dried round-bottom flask. To this was added (+/-)-CSA (1 equiv), and the solution was stirred under argon at rt for 4 h. The solution was then quenched with sat. $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The combined organics were concentrated *in vacuo* without drying, and the crude product mixture was chromatographed (30% EtOAc in hexanes or 50% EtOAc in hexanes, depending on product polarity, see individual procedures vide infra) to separate the desired tris-THP product (always the least polar and therefore the first off the column) from undesired cyclization products.

Representative procedure for reaction promoted by **BF_3**:
A sample of diepoxy alcohol was dissolved in CH_2Cl_2 to 0.02 M in an oven-dried round-bottom flask and cooled to -78 °C. To this was added, dropwise, a 0.1 M solution of BF_3•OEt_2 in CH_2Cl_2 (0.25 equiv), and the solution was stirred at -78 °C under argon for 30 min. The solution was then allowed to warm gradually to rt over 5 min. and quenched with sat. $NaHCO_3$. The aqueous layer was extracted with Et_2O, and the combined

organics were concentrated *in vacuo* without drying. The crude product mixture was chromatographed (30% EtOAc in hexanes or 50% EtOAc in hexanes, depending on product polarity, see individual procedures vide infra) to separate the desired tris-THP product (always the least polar and therefore the first off the column) from undesired cyclization products.



19

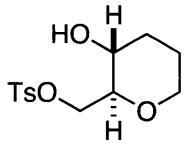
Allylic alcohol 19: Allylic alcohol **19** was prepared according to a procedure modified from that developed by Lebouc, Delaunay, and Riobé.[14] 3,4-Dihydro-2H-pyran (**18**, 120 mL, 112 g, 1.32 mol) was added to a 2 L round-bottom flask, followed by TMEDA (138 mL, 107 g, 0.92 mol). We have found that the reaction works even with undistilled TMEDA directly from the bottle, although yields are approximately 5% higher with TMEDA freshly distilled from CaH_2. After cooling to 0 °C, a 2.5 M solution of *n*BuLi in hexane (370 mL, 0.92 mol) was added slowly, over 15 min. Over the course of addition, the clear, pale yellow solution became cloudier as white solid precipitated, and the color evolved through darker yellow to orange. The reaction was stirred 45 minutes more at 0 °C, over which time the solution turned a vivid, opaque orange. The reaction was then warmed to room temperature and stirred 20 h. Dry THF (600 mL) was then added, at which point the solution turned red-brown. After cooling again to 0 °C, paraformaldehyde ($(CH_2O)_n$) (90 g, 2.96 mol) was added slowly, portionwise, with vigorous stirring, beginning with ~1 g, then ~2 g, then ~4 g, etc., pausing approximately 5 minutes between additions to prevent exotherm. After the addition of paraformaldehyde was complete, the reaction was allowed to warm gradually to room temperature over 20 h., at which point the solution had become a milky, opaque, pale yellow. The reaction was quenched slowly, at room temperature, with sat. NH_4Cl (200 mL) and stirred 15 minutes. The mixture was then diluted with 500 mL of Et_2O. The organic layer was separated, poured over an aqueous solution of $CuSO_4 \cdot 5H_2O$ (250 g in 700 mL H_2O), and stirred vigorously for 30 minutes. The organic layer was then decanted, washed with sat. $NaHCO_3$ (3 x 50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by vacuum distillation (5 torr, bp = 65-71°), and **19** was collected as a clear, colorless oil with an aromatic, woodsy aroma (72 g, 630 mmol, 68%). Allylic alcohol **19** appears unstable to $CDCl_3$ (Cambridge Isotope Laboratories), even after treatment of $CDCl_3$ with K_2CO_3. It is therefore recommended that NMR spectra be recorded in C_6D_6 or another solvent. R_f = 0.61 (50% EtOAc in hexanes). Spectral data was consistent with the sample prepared by Riobé and coworkers.[14]

IR (thin film, NaCl) 3412, 2934, 2874, 1678, 1449, 1239, 1089, 1063, 1025, 893, cm^{-1}.

^1H NMR (400 MHz, C_6D_6) δ 4.74 (t, J = 3.8 Hz, 1H), 4.00-3.94 (broad s, 3H), 3.76 (app t, J = 5.1 Hz, 2 H), 1.78 (app q, J = 6.4, 4.0 Hz, 2 H), 1.47 (app quintet, J = 5.2 Hz, 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, C_6D_6) δ 154.7, 97.1, 66.7, 63.6, 23.3, 20.8.

HR-MS (ESI) *m/z* calcd for $C_6H_{11}O_2$ $(M+Na)^+$: 137.0573, found 137.0579.



20

Tosylate 20: To a stirred solution of allylic alcohol **19** (68 g, 580 mmol) in THF (1300 mL, used directly from the bottle, without drying) maintained at 0 °C was added neat BH_3•SMe_2 (92.5 mL, 925 mmol) gradually, over 20 min. The reaction was stirred 2 h. at 0 °C. Trimethylamine *N*-oxide dihydrate (TMANO•$2H_2O$) (122 g, 1100 mmol) was added at 0 °C slowly, portionwise, with vigorous stirring, beginning with ~3-5 g portions, pausing approximately 5 minutes between additions to prevent exotherm. The reaction was heated to vigorous reflux for 5 h.; over this period white solid clumped along the sides of the flask. The reaction was vacuum filtered while hot to remove all solids; these solids were washed with acetone (4 x 100 mL), and the combined acetone washes and reaction solution were concentrated *in vacuo*. The crude 1,3-diol was left under high vacuum overnight and then used without further purification (R_f = 0.23 in 100% EtOAc).

To a solution of crude diol in CH_2Cl_2 (640 mL, used directly from the bottle, without drying) was added pyridine (183 g, 187 mL, 2300 mmol). After cooling to 0 °C, TsCl (99 g, 520 mmol) was added. The deep yellow solution was maintained at 0 °C for 20 min., then warmed to ambient temperature for 6 h. As TLC indicated incomplete conversion of the diol, a further portion of TsCl (20 g, 105 mmol) was then added. The reaction solution was stirred for a further 15 h. At this point TLC analysis (50% EtOAc in hexanes) implied that conversion of the diol was approx. 90%, with evidence of a trace of ditosylation (R_f of 1,3-diol starting material = 0.07, R_f of tosylate **20** = 0.35, R_f of ditosylate = 0.62). The reaction was quenched at ambient temperature with sat. $NHCO_3$ (300 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The combined organics were washed with sat. NaCl (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Crude **20**, a foul-odored, thin yellow oil, was purified by column chromatography (gradient 25% to 50% to 100% EtOAc in hexanes) to yield tosylate **20** as an odorless, heavy, pale yellow oil that crystallized on standing (67 g, 234 mmol, 40% over 2 steps): R_f = 0.35 (50% EtOAc in hexanes). Spectral data were consistent with that reported for an enantioenriched sample prepared by Delgado and Martin.[41]

IR (KBr pellet) 3532, 3376, 3058, 2948, 2856, 1599, 1342, 1178, 1099, 961, 931 cm^{-1}.

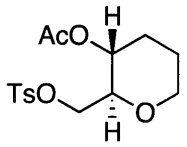
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.34

[41] Delgado, M.; Martin, J. D. *J. Org. Chem.* **1999**, *64*, 4798.

(dd, J = 11.0, 4.5 Hz, 1H), 4.21 (dd, J = 11.0, 2.0 Hz, 1H), 3.91-3.87 (m, 1H), 3.60-3.53 (m, 1H), 3.33-3.27 (m, 1H), 3.22 (ddd, J = 9.3, 4.5, 2.0 Hz, 1H), 2.45 (s, 3H), 2.27 (d, J = 5.5 Hz, 1H), 2.17-2.11 (m, 1H), 1.68-1.63 (m, 2H), 1.47-1.38 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 132.9, 130.0, 128.1, 80.3, 70.1, 68.0, 65.9, 32.5, 25.3, 21.8.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{18}O_5S$ $(M+Na)^+$: 309.0767, found 309.0777.



21

Acetate 21: To a vigorously stirred solution of alcohol **20** (32 g, 112 mmol) in vinyl acetate (48 g, 51 mL, 560 mmol) was added 100 mL of a 3:1 v/v hexanes:THF solution (both directly from the bottle, without drying), followed by Amano lipase PS-C I (immobilized on ceramic, Aldrich catalog #534897) (4.8 g). After having stirred 7 h. at room temperature, the solid beads were filtered off[42] and the filtrate concentrated *in vacuo*. Acetate **21** was separated from **21** via column chromatography (gradient 25% to 30% to 50% to 100% EtOAc in hexanes) to yield enantioenriched acetate **21** as a heavy, pale yellow oil that crystallized on standing (16.2 g, 49 mmol, 44%): R_f = 0.67 (50% EtOAc in hexanes); $[\alpha]^{22}_D$ = -42.9 (c = 8.4, $CHCl_3$). The enantiomeric excess of **21** was determined to be >95% by chiral analytical HPLC analysis (Chiracel OD-H; 12% *i*PrOH in hexanes, 1.30 mL/min; t_R(major) = 12.10 min., t_R(minor) = 13.36 min.).

IR (KBr pellet) 3053, 2978, 2954, 2851, 1733, 1597, 1459, 1360, 1246, 1176, 1062, 1045, 973 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 4.58 (ddd, J = 10.8, 9.8, 4.8 Hz, 1H), 4.14 (dd, J = 10.7, 2.4 Hz, 1H), 4.06 (dd, J = 10.7, 5.6 Hz, 1H), 3.93-3.88 (m, 1H), 3.49 (ddd, J = 9.8, 5.6, 2.4 Hz, 1H), 3.33 (app td, J = 11.6, 2.9 Hz, 1H), 2.45 (s, 3H), 2.26-2.20 (m, 1H), 2.00 (s, 3H), 1.76-1.62 (m, 2H), 1.47-1.38 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 145.0, 132.9, 129.9, 128.2, 76.9, 69.1, 68.1, 68.0, 29.2, 24.8, 21.8, 21.1.

HR-MS (ESI) *m/z* calcd for $C_{15}H_{20}O_6S$ $(M+Na)^+$: 351.0873, found 351.0873.

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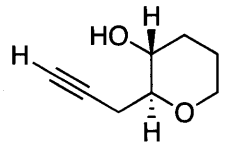
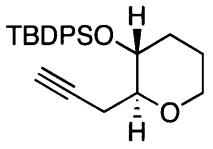
[42] These lipase beads can be reused, as they retain most of their catalytic activity. See: Magnan, E.; Catarino, I.; Paolucci-Jeanjean, D.; Preziosi-Belloy, L.; Belleville, M. P. *J. Membr. Sci.* **2004**, *241*, 161.



17

Alkyne 17: To a flame-dried flask containing fresh lithium acetylide-ethylenediamine complex (10 g, 109 mmol) was added dry THF (210 mL) and freshly distilled DMPU (25 mL) to afford a dusty gray-brown slurry.[43] After cooling to 0 °C, to this solution was added slowly tosylate **21** (5.9 g, 18.1 mmol), over 5 minutes, as a solution in 30 mL DMPU. Any remaining **21** was dissolved with a further 10 mL THF and added via syringe. After stirring 1 h. at 0 °C, the reaction was warmed to room temperature for 34 h. Over time, the solution developed a bright cherry red color, which matured into a rich burgundy red color. Upon recooling to 0 °C, the reaction was quenched with H_2O (150 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL), and the combined organics were washed with sat. NaCl (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (gradient 20% to 40% EtOAc in hexanes) to remove most DMPU and afford bishomopropargylic alcohol **17** as a pale orange oil (1.20 g, 8.6 mmol, 47%): R_f of **17** = 0.55 (50% EtOAc in hexanes); $[\alpha]^{22}_D$ = -16.8 (*c* = 1.9, $CDCl_3$).
Residual DMPU may be removed by further aqueous washes, but **17** is moderately water soluble, and isolated yield will therefore be reduced. Prior to chromatography, crude **17** can be protected as a silyl ether without purification away from DMPU. Residual DMPU promotes silylation, and purification of the much less polar silyl ether is straightforward, resulting in improved yield over this 2-step process; see the synthesis of **22** below.

Spectral data for **17** were consistent with that reported by Bowman and McDonald.[13b]



22

[43] We have found that the yield of this reaction suffers when older lithium acetylide-ethylenediamine complex is used, even if it was stored in a glove box or in a dessicator under argon. Multiple samples of lithium acetylide-ethylenediamine complex sourced from both Alfa Aesar and Sigma-Aldrich have proved adequate, so long as they are used immediately after opening.

Silyl-protected bishomopropargylic alcohol 22: To a flame-dried flask containing fresh lithium acetylide-ethylenediamine complex (23.2 g, 252 mmol) was added dry THF (450 mL) and freshly distilled DMPU (80 mL) to afford a dusty gray-brown slurry.[43] After cooling to 0 °C, to this solution was added slowly tosylate **21** (13.8 g, 42 mmol), over 5 minutes, as a solution in 40 mL DMPU and 20 mL THF. Any remaining **21** was dissolved with a further 10 mL THF and added via syringe. After stirring 1 h. at 0 °C, the reaction was warmed to room temperature for 41 h. Over time, the solution developed a bright cherry red color, which matured into a rich burgundy red color. After recooling to 0 °C, Et_3N (50 mL, 36.3 g, 358 mmol) was added, followed immediately by slow addition of a 1 M solution of HCl in Et_2O (270 mL, 270 mmol). The solution was stirred 10 minutes and vacuum filtered to remove solids; these solids were washed with Et_2O (4 x 100 mL). The combined washes and filtrate were concentrated *in vacuo* to yield a dark red-brown, viscous solution of crude bishomopropargylic alcohol **17** in DMPU, which was used without further purification; R_f of **17** = 0.55 (50% EtOAc in hexanes).

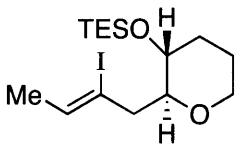
To this solution of alcohol **17** in DMPU was added imidazole (8.6 g, 126 mmol) and TBDPSCl (16.1 mL, 17.3 g, 63 mmol). After warming to 40 °C and stirring for 5 h., the red-brown solution was cooled, diluted with Et_2O (300 mL), and washed with water (400 mL). The aqueous layer was extracted with Et_2O (3 x 150 mL), and the combined organics were washed with sat. NaCl (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was separated from TBDPSOH by column chromatography (gradient 3% to 5% to 10% to 15% EtOAc in hexanes) to afford silyl ether **22** as a pale yellow oil (8.10 g, 21.4 mmol, 51% over 2 steps): R_f = 0.45 (10% EtOAc in hexanes); $[\alpha]^{22}_D$ = -27.4 (*c* = 1.3, $CDCl_3$).

IR (thin film, NaCl) 3310, 2931, 2856, 1428, 1100, 1047 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.74-7.68 (m, 4H), 7.47-7.42 (m, 2H), 7.39 (app t, *J* = 7.1 Hz, 4 H), 3.91-3.86 (m, 1H), 3.55 (ddd, *J* = 9.6, 4.7, 4.7 Hz, 1H), 3.38-3.31 (m, 2H), 2.77 (app dt, *J* = 16.9, 2.9 Hz, 1H), 2.48 (ddd, *J* = 16.9, 6.8, 2.7 Hz, 1H), 1.98 (app t, *J* = 2.7 Hz, 1H), 1.81-1.73 (m, 1H), 1.49-1.40 (m, 3H), 1.05 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.7, 133.4, 130.0, 129.8, 127.9, 127.6, 81.6, 80.8, 71.4, 69.7, 68.2, 33.3, 27.2, 25.5, 22.5, 19.5.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{30}O_2Si$ $(M+Na)^+$: 401.1907, found 401.1924.



23

Alkenyl iodide 23: To a solution of bishomopropargylic alcohol **17** (265 mg, 1.89 mmol) in CH_2Cl_2 (20 mL) at -78 °C was added slowly a 2 M solution of $AlMe_3$ in hexanes (2.08 mL, 4.16 mmol). This solution was warmed for 3 min. by removing the flask from its cold bath to ensure complete deprotonation. After recooling to -78 °C, a 1 M solution of $TiCl_4$ in CH_2Cl_2 (2.08 mL, 2.08 mmol) was added dropwise, during which time the solution turned maroon, then a deep red. The solution was stirred 2 h. at -78 °C and then quenched with a solution of I_2 (2.4 g, 9.45 mmol) in Et_2O (20 mL). The reaction flask was then wrapped in foil and allowed to warm to room temperature for 10 h., at which point H_2O (2 mL) was added. The quenched reaction solution was diluted with Et_2O (100 mL) and washed with aqueous 3 M $NaHSO_3$ (40 mL) until the organic layer was colorless. The aqueous layer was extracted with Et_2O (3 x 40 mL), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. The crude alkenyl iodide was carried forward without purification; R_f = 0.72 (50% EtOAc in hexanes), UV active.

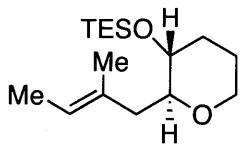
Upon dissolution of this crude alkenyl iodide in DMF (1 mL), imidazole (322 mg, 4.73 mmol) and TESCl (380 μL, 342 mg, 2.27 mmol) were added, and the solution was stirred 2 h. at room temperature. The reaction was applied directly to column of SiO_2 and chromatographed (2% EtOAc in hexanes) to afford protected alkenyl iodide **23** (310 mg, 0.78 mmol, 41% over 2 steps), which was isolated along with some silylated bishomopropargylic alcohol (43 mg, 0.17 mmol). R_f of **23** = 0.60 (10% EtOAc in hexanes), UV active; $[\alpha]^{22}_D$ = -19.2 (*c* = 4.0, $CHCl_3$).

IR (thin film, NaCl) 2955, 2876, 1461, 1415, 1274, 1239, 1127, 1102, 1004 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 5.64 (app qt, *J* = 6.3, 0.7 Hz, 1H), 3.90-3.85 (m, 1H), 3.39-3.28 (m, 3H), 3.04 (app d, *J* = 14.8 Hz, 1H), 2.41 (dd, *J* = 14.8, 9.1 Hz, 1H), 2.02 (m, 1H), 1.75 (d, *J* = 6.3 Hz, 3H), 1.68-1.62 (m, 2H), 1.54-1.44 (m, 1H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 7.8 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 131.5, 107.3, 81.3, 70.8, 68.1, 47.8, 33.8, 25.8, 22.5, 7.1, 5.3.

HR-MS (ESI) *m/z* calcd for $C_{15}H_{29}IO_2Si$ $(M+Na)^+$: 419.0874, found 419.0893.



24

Trisubstituted alkene 24: To a sealed tube charged with $Pd(PPh_3)_4$ (60 mg, 0.045 mmol) was added 5 mL THF to provide a clear lemon yellow solution. Upon cooling to 0 °C,

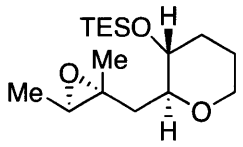
alkenyl iodide **23** (410 mg, 1.03 mmol) was added as a solution in THF (2 mL), followed immediately by a 2.0 M solution of Me_2Zn in PhMe (1.55 mL, 3.10 mmol) to provide a paler yellow solution. The tube was sealed and the temperature was maintained at 0 °C for 1 h. and then warmed to room temperature for 12 h. The reaction was diluted with Et_2O (10 mL) and quenched by pouring slowly over 10 mL H_2O. The aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to give an orange-brown crude oil. This crude product was purified by column chromatography (gradient 1% to 2.5% to 10% EtOAc in hexanes) to afford **24** as a colorless oil (250 mg, 0.88 mmol, 85%): R_f = 0.66 (10% EtOAc in hexanes); $[\alpha]^{22}_D$ = -17.8 (*c* = 0.38, $CDCl_3$).

IR (thin film, NaCl) 2952, 2924, 2876, 1460, 1127, 1098, 1017 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 5.29 (app q, *J* = 6.7 Hz, 1H), 3.91-3.87 (m, 1H), 3.32-3.26 (m, 2H), 3.19 (ddd, *J* = 10.4, 8.7, 2.2, 1H), 2.62 (app d, *J* = 14.3 Hz, 1H), 2.04-1.99 (m, 1H), 1.95 (dd, *J* = 14.4, 10.1, 1H), 1.72-1.58 (m, 8H), 1.51-1.42 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 133.6, 120.4, 81.2, 71.7, 68.0, 42.7, 33.9, 25.9, 15.8, 13.8, 7.1, 5.3.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{32}O_2Si$ $(M+Na)^+$: 307.2064, found 307.2067.



S1

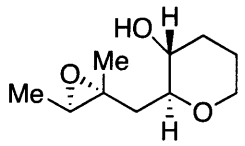
Epoxide S1: To a solution of alkene **24** (224 mg, 0.79 mmol) in 2:1 v/v DMM:MeCN (25.7 mL) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} Na_2EDTA (16.6 mL), $n$$Bu_4HSO_4$ (54 mg, 0.16 mmol), and chiral ketone **25** (405 mg, 1.57 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 30 min. via syringe pump, a solution of Oxone (1.94 g, 3.16 mmol) in 4 x 10^{-4} Na_2EDTA (13.1 mL) and a 0.89 M solution of K_2CO_3 (13.1 mL, 11.7 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 25 min., at which point it was diluted with EtOAc (40 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to provide **S1** in a 2.8:1 diastereomeric mixture. The desired diastereomer (R_f = 0.55, 20% EtOAc in hexanes) was separated from the undesired diastereomer (R_f = 0.59, 20% EtOAc in hexanes) and ketone catalyst **25** by patient column chromatography (gradient 2% to 3% to 5% EtOAc in hexanes) to afford epoxide **S1** in >15:1 dr as a colorless oil (159 mg, 0.53 mmol, 67%): R_f = 0.55 (20% EtOAc in hexanes); $[\alpha]^{22}_D$ = -37.8 (*c* = 0.45, $CDCl_3$).

IR (thin film, NaCl) 2956, 2877, 1458, 1127, 1099, 1009 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 3.91-3.86 (m, 1H), 3.34-3.23 (m, 2H), 3.12 (app td, J = 8.9, 1.7 Hz, 1H), 2.89 (q, J = 5.5 Hz, 1H), 2.09 (dd, J = 14.6, 1.6 Hz, 1H), 2.04-1.98 (m, 1H), 1.72-1.61 (m, 2H), 1.57 (dd, J = 14.6, 9.9 Hz, 1H), 1.49-1.36 (m, 1H), 1.30 (s, 3H), 1.29 (d, J = 5.5 Hz, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.59 (q, J = 8.1 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 80.4, 71.1, 67.7, 59.8, 58.2, 40.6, 33.8, 25.8, 17.6, 14.3, 7.1, 5.3.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{32}O_3Si$ $(M+Na)^+$: 323.2013, found 323.2010.



15

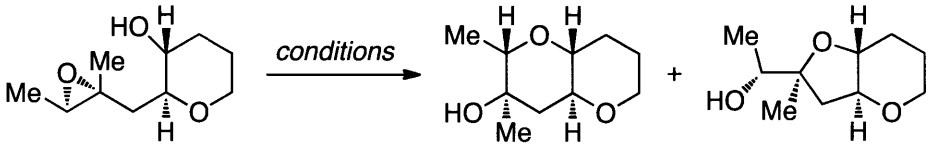
Epoxy alcohol 15: To a solution of TES-protected epoxy alcohol **S1** (17.5 mg, 0.058 mmol, in >20:1 dr) in THF (1.0 mL) cooled to 0 °C was added a 1 M THF solution of TBAF (70 μL, 0.070 mmol). The reaction was stirred for 20 min. at 0 °C. While still cold, the crude product in THF was applied directly to a SiO_2 column (SiO_2 packed in 2% Et_3N dissolved in 20% EtOAc in hexanes, run with a gradient from 2% Et_3N dissolved in 20% EtOAc in hexanes to 50% EtOAc in hexanes) and concentrated *in vacuo* to afford epoxy alcohol **15** as a colorless oil (9.8 mg, 0.053 mmol, 90%): R_f = 0.54 (100% EtOAc); $[\alpha]^{22}_D$ = -9.7 (*c* = 0.20, $CDCl_3$). This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize traces of DCl in $CDCl_3$ with K_2CO_3 before collecting NMR data. **15** cyclizes very slowly on standing at -20 °C in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -20 °C as a neat oil. For extended periods, **15** is best stored frozen in benzene at -20 °C.

IR (thin film, NaCl) 3417, 2926, 2851, 1723, 1462, 1381, 1274, 1096 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.94-3.88 (m, 1H), 3.48 (app td, J = 9.9, 4.1 Hz, 1H), 3.34-3.27 (m, 1H), 3.13 (ddd, J = 9.3, 6.8, 2.8 Hz, 1H), 2.96 (q, J = 5.5 Hz, 1H), 2.61 (broad s, 1H), 2.20-2.09 (m, 2H), 1.77-1.65 (m, 3H), 1.45-1.33 (m, 4H), 1.31 (d, J = 5.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 80.5, 69.8, 68.1, 60.1, 59.0, 40.5, 32.6, 26.0, 17.6, 14.0.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1153.



15 32 33

Cyclization of 15 to 32 and 33:

Representative procedure for reaction in **aqueous media:**
Epoxy alcohol **15** (1 mg, 0.0054 mmol) was dissolved either in deionized water (270 μL) or 1 M solution of potassium phosphate buffer in deionized water (270 μL) and stirred at rt under air for 3 d. At this point the crude product mixture was extracted with EtOAc (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **32** to **33**. For reactions in deionized water, **32**:**33** was found to be 4.9:1 (average of 6 experiments).

Dependence of Regioselectivity on pH in Reactions of **15**

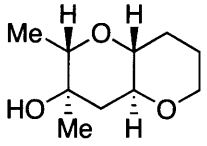
entry	pH (1.0 M KP_i buffer)	**32**:**33** observed
1	1.8	0.11:1
2	3.9	0.14:1
3	6.0	0.51:1
4	7.0	1.9:1
5	7.2	2.0:1
6	7.2	1.9:1
7	8.0	4.3:1
8	8.0	4.4:1
9	8.5	5.3:1
10	9.0	3.4:1
11	9.4	5.9:1
12	9.5	5.8:1
13	10.0	4.3:1
14	10.7	3.0:1
15	11.0	4.0:1
16	11.8	2.3:1
17	12.0	3.6:1
18	12.5	2.1:1
19	12.5	2.9:1

Procedure for reaction under **Cs_2CO_3 promotion:**
To a solution of epoxy alcohol **15** (1 mg, 0.0054 mmol) in MeOH (270 μL) was added Cs_2CO_3 (53 mg, 0.16 mmol) and stirred at rt under air for 3 d. At this point the crude product mixture was diluted with deionized water (500 μL), extracted with EtOAc (5x2

mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **32** to **33** to be 3.0:1.

Procedure for reaction under **CSA promotion:**
To a solution of epoxy alcohol **15** (1 mg, 0.0054 mmol) in CH_2Cl_2 (270 μL) was added (+/-)-CSA (1.3 mg, 0.0056 mmol) and stirred at rt under argon for 4 h. At this point the crude product mixture was diluted with CH_2Cl_2 (2 mL) and washed with sat. $NaHCO_3$ (500 μL). The aqueous layer was extracted with CH_2Cl_2 (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **32** to **33** to be 1:5.2.

Procedure for reaction under **BF_3 promotion:**
To a solution of epoxy alcohol **15** (1 mg, 0.0054 mmol) in CH_2Cl_2 (270 μL) cooled to -78 °C was added, dropwise, a stock solution of 0.1 M BF_3•OEt_2 in CH_2Cl_2 (14 μL, 0.0014 mmol) and stirred at -78 °C under argon for 30 min. At this point the reaction was allowed to warm gradually to rt over 5 min., diluted with CH_2Cl_2 (2 mL), and quenched with sat. $NaHCO_3$ (500 μL). The aqueous layer was extracted with CH_2Cl_2 (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **32** to **33** to be 1:11.



32

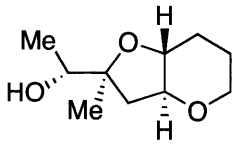
bis-THP 32: R_f = 0.55 (100% EtOAc).

$[\alpha]^{22}_D$ = -12.7 (*c* = 0.87, $CDCl_3$).

IR (thin film, NaCl) 3434, 2941, 2867, 1717, 1457, 1377, 1354, 1286, 1106, 1077, 1031, 964, 943 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.94-3.88 (m, 1H), 3.41-3.34 (m, 2H), 3.07-2.97 (m, 2H), 2.12 (dd, *J* = 11.5, 4.2 Hz, 1H), 2.10-2.04 (m, 1H), 1.75-1.68 (m, 2H), 1.57 (app t, *J* = 11.3 Hz, 1H), 1.50-1.41 (m, 2H), 1.23 (s, 3H), 1.18 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.5, 78.9, 77.2, 71.5, 68.1, 45.9, 29.6, 25.8, 21.3, 14.4.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1157.



33

6,5-fused 33: $R_f = 0.45$ (100% EtOAc).

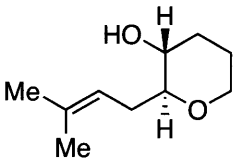
$[\alpha]^{22}_D = -29.0$ ($c = 0.03$, $CDCl_3$).

IR (thin film, NaCl) 3436, 2923, 2850, 1728, 1463, 1377, 1261, 1126, 1068 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$) δ 4.00 (app dd, J = 11.6, 4.8 Hz, 1H), 3.77 (qd, J = 6.5, 3.0 Hz, 1H), 3.48 (app td, J = 11.9, 3.1 Hz, 1H), 3.37 (ddd, J = 11.1, 9.1, 3.8 Hz, 1H), 3.31 (ddd, J = 11.1, 9.0, 6.3 Hz, 1H), 2.24-2.20 (m, 1H), 2.16 (app t, J = 11.0 Hz, 1H), 1.82 (dd, J = 11.1, 6.3 Hz, 1H), 1.74-1.61 (m, 2H), 1.56-1.48 (m, 1H), 1.22 (s, 3H), 1.15 (d, J = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 84.7, 81.0, 80.0, 73.6, 69.0, 35.1, 30.4, 25.7, 24.8, 17.7.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1154, found 209.1153.



27

Trisubstituted alkene 27: To a solution of TMS ether **21** (207 mg, 0.92 mmol) in THF (9 mL) was added a 1 M aqueous solution of HCl (7 mL, 7 mmol). The mixture was stirred at room temperature for 15 min., diluted with Et_2O (30 mL), and then quenched with sat. $NaHCO_3$ (15 mL). The aqueous layer was extracted with Et_2O (3 x 25 ml), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. The crude free alcohol ($R_f = 0.56$ in 50% EtOAc in hexanes) was pumped on under high vacuum for 2 h. to remove residual TMSOH and then carried forward without further purification.

To a solution of this crude bishomopropargylic alcohol in CH_2Cl_2 (10 mL) at 0 °C was added slowly a 2 M solution of $AlMe_3$ in hexanes (0.96 mL, 1.93 mmol). This solution was stirred for 3 min. and then recooled to -78 °C. A 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.96 mL, 0.96 mmol) was added dropwise, during which time the solution turned maroon, then a deep red. The solution was stirred 2 h. at -78 °C and then quenched with

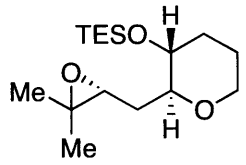
cold MeOH (1 mL), upon which the solution turned pale yellow. The solution was diluted with Et_2O (10 mL) and washed with a saturated solution of Rochelle's salt (10 mL). The aqueous layer was extracted with Et_2O (3 x 20 ml), dried over $MgSO_4$, and concentrated *in vacuo*, and this crude product was purified by column chromatography (25% EtOAc in hexanes) to afford trisubstituted alkene **27** as a colorless oil (105 mg, 0.62 mmol, 67% over 2 steps): R_f = 0.38 (30% EtOAc in hexanes); $[\alpha]^{22}_D$ = -19.4 (*c* = 1.2, $CDCl_3$). Some unreacted bishomopropargylic alcohol (16 mg, 0.10 mmol, 12%) was also recovered.

IR (thin film, NaCl) 3412, 2928, 2855, 1451, 1376, 1340, 1277, 1095, 1036, 944 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 5.29 (app t, *J* = 7.0 Hz, 1H), 3.94-3.89 (m, 1H), 3.42-3.30 (m, 2H), 3.08 (ddd, *J* = 8.7, 7.2, 4.5 Hz, 1H), 2.52 (app dt, *J* = 15.0, 5.8 Hz, 1H), 2.24 (app dt, *J* = 15.0, 7.0 Hz, 1H), 2.10 (m, 1H), 1.73 (s, 3H), 1.72-1.64 (m, 5H), 1.40 (dddd, *J* = 17.4, 11.3, 6.3, 5.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 120.5, 82.4, 70.9, 67.9, 32.8, 31.6, 26.1, 25.7, 18.2.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_2$ $(M+Na)^+$: 193.1199, found 193.1194.



28

Epoxide 28: Upon dissolution of bishomoallylic alcohol **27** in DMF (1 mL), imidazole (105 mg, 1.54 mmol) and TESCl (130 μL, 116 mg, 0.77 mmol) were added, and the solution was stirred 6 h. at room temperature. The reaction was applied directly to a plug of SiO_2 and quickly flushed (3% EtOAc in hexanes) to afford the bishomopropargylic silyl ether (128 mg, 0.45 mmol, 74%), which was carried forward without further purification.

To a solution of this protected bishomopropargylic silyl ether (125 mg, 0.45 mmol) in 2:1 v/v DMM:MeCN (14.7 mL) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} Na_2EDTA (9.5 mL), nBu_4HSO_4 (31 mg, 0.09 mmol), and chiral ketone **25** (232 mg, 0.91 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 30 min. via syringe pump, a solution of Oxone (1.12 g, 1.82 mmol) in 4 x 10^{-4} Na_2EDTA (7.5 mL) and a 0.89 M solution of K_2CO_3 (7.5 mL, 6.7 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 25 min., at which point it was diluted with EtOAc (25 mL). The aqueous layer was extracted with EtOAc (3 x 25 mL), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to provide a 5.8:1

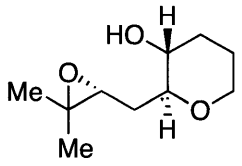
diastereomeric mixture of epoxides. The desired epoxide diastereomer was inseparable from the undesired, but the combined epoxide diastereomers were separated from ketone catalyst **25** by column chromatography (5% EtOAc in hexanes) to afford epoxide **28** in 5.8:1 dr as a colorless oil (110 mg, 0.37 mmol, 73% combined): R_f = 0.66 (20% EtOAc in hexanes). All characterization was obtained on this 5.8:1 mixture of diastereomers: $[\alpha]^{22}_D$ = -44.6 (*c* = 2.85, $CDCl_3$).

IR (thin film, NaCl) 2956, 2877, 1458, 1377, 1240, 1099, 1016 cm^{-1}.

Tabulated ^1H and ^{13}C NMR shifts and coupling constants are reported for the major diastereomer:
^1H NMR (500 MHz, $CDCl_3$) δ 3.93-3.87 (m, 1H), 3.38-3.29 (m, 2H), 3.14 (app td, *J* = 8.9, 2.7 Hz, 1H), 2.94 (app t, *J* = 3.0 Hz, 1H), 2.06-1.98 (m, 2H), 1.72-1.60 (m, 3H), 1.49-1.38 (m, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 81.6, 71.3, 67.9, 62.0, 57.5, 33.8, 32.2, 25.8, 25.1, 18.9, 7.0, 5.3.

HR-MS (ESI) *m/z* calcd for $C_{16}H_{32}O_3Si$ $(M+Na)^+$: 323.2013, found 323.2023.



16

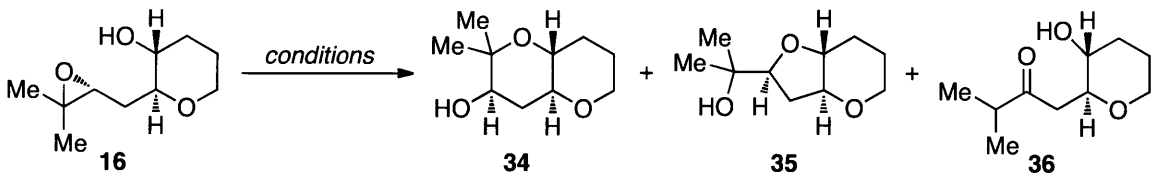
Epoxy alcohol 16: To a solution of TES-protected epoxy alcohol **16** (33 mg, 0.11 mmol, in a 5.8:1 diastereomeric mixture) in THF (1.5 mL) cooled to 0 °C was added a 1 M THF solution of TBAF (130 μL, 0.13 mmol). The reaction was stirred for 10 min. at 0 °C. While still cold, the crude product in THF was applied directly to a SiO_2 column (SiO_2 packed in 2% Et_3N dissolved in 20% EtOAc in hexanes, run with a gradient from 2% Et_3N dissolved in 20% EtOAc in hexanes to 50% EtOAc in hexanes) and concentrated *in vacuo* to afford epoxy alcohol **16** as a colorless oil (20 mg, 0.11 mmol, 98%) as an inseparable 5.8:1 mixture of diastereomers: R_f = 0.54 (100% EtOAc in hexanes). This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize traces of DCl in $CDCl_3$ with K_2CO_3 before collecting NMR data. Epoxy alcohol **16** cyclizes very slowly on standing at -20 °C in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -20 °C as a neat oil. For extended periods, **16** is best stored frozen in benzene at -20 °C. All characterization for epoxy alcohol **16** was obtained on this 5.8:1 mixture of diastereomers: $[\alpha]^{22}_D$ = -2.1 (*c* = 1.0, $CDCl_3$).

IR (thin film, NaCl) 3427, 2930, 2854, 1656, 1461, 1379, 1347, 1273, 1097, 1042, 971 cm^{-1}.

Tabulated ^1H and ^{13}C NMR shifts and coupling constants are reported for the major diastereomer:
^1H NMR (500 MHz, $CDCl_3$) δ 3.96-3.90 (m, 1H), 3.61-3.54 (m, 1H), 3.37 (app td, J = 11.3, 3.7 Hz, 1H), 3.24 (ddd, J = 9.0, 5.7, 3.1 Hz, 1H), 3.03 (dd, J = 8.8, 3.1 Hz, 1H), 2.37-2.33 (m, 1H), 2.15-2.05 (m, 2H), 1.80-1.66 (m, 4H), 1.48-1.38 (m, 1H), 1.33 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 81.2, 69.7, 68.2, 61.2, 58.3, 32.4, 31.7, 26.0, 25.0, 19.0.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1155.



Reaction of epoxy alcohol 16 to products 34, 35, and 36:

Representative procedure for reaction in **aqueous media:**
Epoxy alcohol **16** (1.5 mg, 0.0080 mmol) was dissolved either in deionized water (420 μL) or 1 M solution of potassium phosphate buffer in deionized water (420 μL) and stirred at rt under air for 3 d. At this point the crude product mixture was extracted with EtOAc (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^1H NMR spectroscopy to determine the ratio of **34** to **35** to **36**. For reactions in deionized water, **34**:**35** was found to be 25:1, 30:1, and 34:1 in separate experiments, with no **36** observed.

Dependence of Regioselectivity on pH in Reactions of **16**

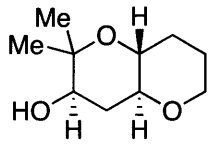
entry	pH (1 M KP_i buffer)	**34**:**35**:**36**
1	1.8	22:1:1
2	3.9	24:1:1
3	6.0	32:1:1
4	7.1	19:1:0
5	7.2	37:1:0
6	8.0	26:1:0
7	8.1	25:1:0
8	9.0	14:1:0
9	9.9	3.5:1:0
10	10.0	2.8:1:0

11	10.5	1.0:1:0
12	10.9	0.49:1:0
13	11.8	0.14:1:0
14	12.0	0.29:1:0

Procedure for reaction under **Cs_2CO_3 promotion:**
To a solution of epoxy alcohol **16** (1.5 mg, 0.0080 mmol) in MeOH (420 μL) was added Cs_2CO_3 (78 mg, 0.24 mmol) and stirred at rt under air for 3 d. At this point the crude product mixture was diluted with deionized water (500 μL), extracted with EtOAc (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **34** to **35** to be 1:17, with no trace of **36**.

Procedure for reaction under **CSA promotion:**
To a solution of epoxy alcohol **16** (1.5 mg, 0.0080 mmol) in CH_2Cl_2 (420 μL) was added (+/-)-CSA (1.9 mg, 0.0080 mmol) and stirred at rt under argon for 4 h. At this point the crude product mixture was diluted with CH_2Cl_2 (2 mL) and washed with sat. $NaHCO_3$ (500 μL). The aqueous layer was extracted with CH_2Cl_2 (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio **34**:**35**:**36** to be 5.8:1:0.5.

Procedure for reaction under **BF_3 promotion:**
To a solution of epoxy alcohol **16** (1.5 mg, 0.0080 mmol) in CH_2Cl_2 (420 μL) cooled to -78 °C was added, dropwise, a stock solution of 0.1 M BF_3•OEt_2 in CH_2Cl_2 (20 μL, 0.0020 mmol) and stirred at -78 °C under argon for 30 min. At this point the reaction was allowed to warm gradually to rt over 5 min., diluted with CH_2Cl_2 (2 mL), and quenched with sat. $NaHCO_3$ (500 μL). The aqueous layer was extracted with CH_2Cl_2 (5x2 mL) and concentrated *in vacuo* without drying. The crude product mixture was analyzed by ^{1}H NMR spectroscopy to determine the ratio of **34** to ketone **36** to be 2.2:1, with no trace of *exo* product **35**.



34

bis-THP 34: R_f = 0.54 (100% EtOAc).

$[\alpha]^{22}_D$ = +15.8 (*c* = 0.85, $CDCl_3$).

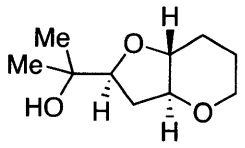
IR (thin film, NaCl) 3440, 2943, 2868, 1711, 1464, 1377, 1281, 1217, 1159, 1068, 1030,

998, 940 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.94-3.88 (m, 1H), 3.53 (app dt, J = 11.6, 4.7 Hz, 1H), 3.41-3.34 (m, 1H), 3.21 (ddd, J = 11.0, 9.2, 4.2 Hz, 1H), 2.96 (ddd, J = 11.6, 9.2, 4.4 Hz, 1H), 2.13 (app dt, J = 11.6, 4.5 Hz, 1H), 1.99-1.93 (m, 1H), 1.77-1.68 (m, 2H), 1.66-1.55 (m, 2H), 1.43-1.33 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 78.0, 75.9, 73.5, 70.7, 68.2, 35.1, 29.9, 28.0, 25.9, 16.8.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1152.



35

6,5-fused 35: R_f = 0.50 (100% EtOAc).

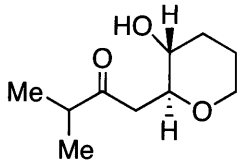
$[\alpha]^{22}_D$ = -5.8 (c = 0.41, $CDCl_3$).

IR (thin film, NaCl) 3447, 2945, 2871, 1465, 1382, 1278, 1127, 1085, 1068, 967 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 4.02-3.97 (m, 1H), 3.92 (dd, J = 9.9, 6.3 Hz, 1H), 3.47 (app td, J = 11.9, 3.2 Hz, 1H), 3.33-3.21 (m, 2H), 2.25-2.19 (m, 1H), 2.13 (app dt, J = 11.2, 6.1 Hz, 1H), 1.97 (broad s, 1H), 1.90 (app q, J = 10.8 Hz, 1H), 1.75-1.60 (m, 1H), 1.52 (app qd, J = 11.5, 4.7 Hz, 1H), 1.24 (s, 3H), 1.17 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 83.6, 81.4, 79.0, 72.5, 68.9, 31.2, 30.0, 26.6, 24.7, 24.1.

HR-MS (ESI) *m/z* calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1156.



36

Isopropyl ketone 36: R_f = 0.56 (100% EtOAc).

$[\alpha]^{22}_D$ = -15.3 (c = 0.08, $CDCl_3$).

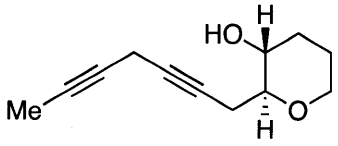
IR (thin film, NaCl) 3415, 2925, 2853, 1708, 1466, 1383, 1273, 1096, 1028, 947 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$) δ 3.89-3.84 (m, 1H), 3.52 (ddd, J = 9.1, 6.8, 4.8 Hz, 1H), 3.38-3.29 (m, 2H), 2.90 (dd, J = 16.3, 4.7 Hz, 1H), 2.74 (dd, J = 16.3, 6.8 Hz, 1H), 2.67 (septet, J = 6.9 Hz, 1H), 2.18-2.12 (m, 1H), 1.98 (d, J = 6.2 Hz, 1H), 1.75-1.66 (m, 2H), 1.46-1.38 (m, 1H), 1.12 (d, J = 6.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 78.8, 71.1, 68.0, 44.5, 41.8, 33.5, 29.9, 25.8, 18.1.

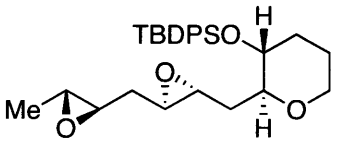
HR-MS (ESI) m/z calcd for $C_{10}H_{18}O_3$ $(M+Na)^+$: 209.1148, found 209.1156.

HR-MS (EI) m/z calcd for $C_{12}H_{21}O_4$ $(M+H)^+$: 229.1440, found 229.1436.



39

Diyne 39: This compound was prepared via a previously published 1-step procedure from terminal alkyne **17**.[26]



40

Diepoxide 40: A solution of diyne **39** (540 mg, 2.81 mmol) in THF (5 mL) was cooled to -40 °C, into which flask NH_3 gas was condensed (~60 mL). To this solution was added dry MeOH (2.3 mL, 1.8 g, 56 mmol). Lithium metal (120 mg, 18.6 mmol, cut into 10-20 mg pieces from Li^0 wire washed with hexanes) was added portionwise, allowing one minute between additions. With each addition, a blue "tail" developed behind each piece

of Li^0 as the metal swirled and dissolved into solution. The blue color gradually disappeared as the metal was consumed, at which point the next piece of Li^0 was added. With the addition of the last piece, the blue was more persistent, lasting 3-5 min. before disappearing, at which point the reaction was quenched (vide infra). At no point did the reaction solution become a completely homogenous deep blue color. We believe that overreduction of the diene can be a major problem, resulting in low or even 0% yields, and that it is therefore critical to use a smaller excess of Li^0 than is typically used in dissolving metal reductions. The reaction was quenched at -40 °C via slow addition of solid NH_4Cl (~20 g) and allowed to warm gradually to room temperature. The resulting solid residue was dissolved in Et_2O (50 mL) and water (25 mL). The aqueous layer was separated and extracted with Et_2O (3x50 mL), and combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to afford a crude mixture of 1,4-diene as well as some monoene overreduction products as a colorless oil: R_f for all = 0.68 (50% EtOAc in hexanes). This moderately unstable material was carried forward into silyl protection without further purification.

To a solution of this crude diene in DMF (3 mL) was added imidazole (478 mg, 7.0 mmol) and TBDPSCl (860 μL, 920 mg, 3.37 mmol), and the resulting solution was stirred at rt for 1 h., at which point it was quenched with sat. $NaHCO_3$ (~3 mL) and diluted with Et_2O (~10 mL) and water (~10 mL). The aqueous layer was separated and extracted with Et_2O (3x40 mL), and combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to afford the moderately unstable crude silyl-protected 1,4-diene: R_f = 0.70 (10% EtOAc in hexanes), which was carried forward into Shi epoxidation without further purification.

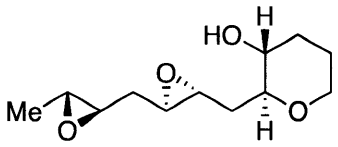
To this crude mixture in 2:1 v/v DMM:MeCN (237 mL) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} Na_2EDTA (158 mL), nBu$_4HSO_4$ (238 mg, 0.70 mmol), and chiral ketone **25** (1.45 g, 5.6 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 30 min. via syringe pump, a solution of Oxone (17.3 g, 28 mmol) in 4 x 10^{-4} Na_2EDTA (79 mL) and a 0.89 M solution of K_2CO_3 (79 mL, 70 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 30 min., at which point it was diluted with EtOAc (~400 mL) and water (~100 mL). The aqueous layer was separated and extracted with EtOAc (3x500 mL), and the combined organics were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. NMR and TLC evidence at this point indicated approx. 75% conversion of the diene. This partially oxidized reaction mixture was then subjected again to identical epoxidation conditions and worked up as before. After resubjection, crude diepoxide **40** was chromatographed (gradient 10% to 20% to 30% EtOAc in hexanes) to provide **40**, a colorless oil, as an inseparable mixture of diastereomers (371 mg of a 2.5:1 overall diastereomeric mixture, 0.79 mmol combined, 28% over 3 steps): R_f = 0.29 (20% EtOAc in hexanes). Diepoxide **40** was further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.6% *i*PrOH in hexanes, 30 mL/min.; t_R of desired diastereomer = 9.0 min.) to afford **40** in 20:1 overall dr: $[\alpha]^{22}_D$ = +4.2 (*c* = 2.4, $CDCl_3$).

IR (thin film, NaCl) 3072, 2958, 2931, 2857, 1472, 1428, 1380, 1361, 1103 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.70-7.65 (m, 4H), 7.47-7.36 (m, 6H), 3.84-3.78 (m, 1H), 3.43-3.36 (m, 1H), 3.33-3.26 (m, 2H), 2.86-2.79 (m, 4H), 2.05 (ddd, J = 14.4, 5.6, 2.6 Hz, 1H), 1.84-1.76 (m, 2H), 1.72-1.62 (m, 2H), 1.51-1.37 (m, 3H), 1.33 (d, J = 5.1 Hz, 3H), 1.03 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.7, 133.6, 130.0, 129.8, 127.9, 127.6, 80.8, 72.2, 67.8, 56.9, 56.5, 55.0, 54.6, 35.4, 34.7, 33.5, 27.2, 25.6, 19.5, 17.8.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_4Si$ $(M+Na)^+$: 489.2432, found 489.2447.



37

Diepoxy alcohol 37: To a solution of silyl ether **40** (66 mg, 0.14 mmol, in 20:1 overall dr) in THF (900 μL) was added a 1 M solution of TBAF in THF (280 μL, 0.28 mmol). The reaction was warmed to 30 °C for 2 h., cooled, and filtered through a pad of SiO_2 (gradient 20% to 50% to 100% EtOAc in hexanes) to yield free diepoxy alcohol **37** as a colorless oil (32.8 mg, 0.14 mmol, 99%): R_f = 0.41 (100% EtOAc); $[\alpha]^{22}_D$ = +39.4 (c = 1.6, $CDCl_3$).[S44] This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize traces of DCl in $CDCl_3$ with K_2CO_3 before collecting NMR data. Diepoxy alcohol **37** cyclizes very slowly on standing at -20 °C in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -20 °C as a neat oil. For extended periods, **37** is best stored frozen in benzene at -20 °C.

IR data was consistent with that previously reported.[26]

^1H NMR data was consistent with that previously reported.[26] We nevertheless retabulate ^1H NMR data here, as the improved diastereopurity of **37** has enabled the determination of coupling constants not previously measurable: ^1H NMR (500 MHz, $CDCl_3$) δ 3.93-3.88 (m, 1H), 3.52 (ddd, J = 10.8, 9.5, 4.5 Hz, 1H), 3.38-3.31 (m, 1H), 3.18 (ddd, J = 9.2, 5.9, 3.4 Hz, 1H), 2.99 (ddd, J = 7.7, 3.1, 2.5 Hz, 1H), 2.89 (ddd, J = 6.8, 4.6, 2.3 Hz, 1H), 2.83-2.78 (m, 2H), 2.28 (broad s, 1H), 2.16-2.07 (m, 2H), 1.82-1.65 (m, 5H), 1.41 (dddd, J = 12.2, 11.6, 11.1, 5.3 Hz, 1H), 1.31 (d, J = 5.0 Hz, 3H).

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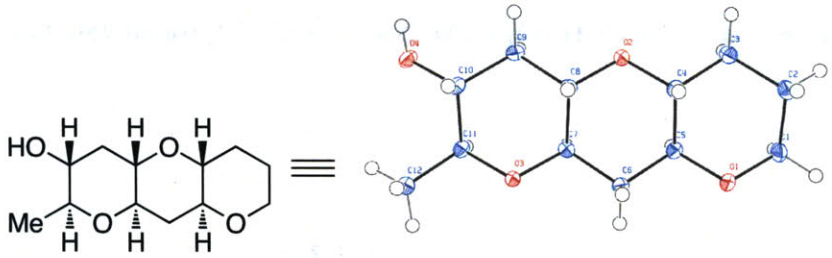
[44] This specific rotation ($[\alpha]^{22}_D$ = +39.4 (c = 1.6, $CDCl_3$)), measured on a sample of material in 20:1 diastereopurity, differs from the value reported earlier by our group, which was measured on a sample in 4:1 dr ($[\alpha]^{25}_D$ = +2.3 (c = 0.7, CDCl3)).[26]

^{13}C NMR data was consistent with that previously reported.[26] However, all ^{13}C shift values for **37** in ref. 26 are off by 0.4-0.5 ppm due to an incorrectly referenced $CDCl_3$ center peak. We therefore retabulate ^{13}C NMR data here: ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.6, 69.9, 68.1, 56.7, 55.8, 55.4, 54.7, 35.1, 34.9, 32.6, 26.0, 17.7.

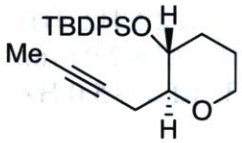


38

Cascade reaction of diepoxy alcohol 37 to THP triad 38:

Reaction in **water**: Diepoxy alcohol **37** (22.8 mg, 0.100 mmol, in 20:1 dr) was dissolved in deionized water (5.0 mL) in a 20 mL vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60 °C under air for 3 d. The solution was then cooled to rt and concentrated *in vacuo* (10 torr, 40 °C). The crude product mixture was chromatographed (50% EtOAc in hexanes) to separate the desired tris-THP **38** (16.8 mg, 0.074 mmol, 74% (78% adjusted for 20:1 dr), a white crystalline solid) from side products.

Spectral data were consistent with that previously reported.[13a,26] We have corroborated the connectivity and the relative and absolute configurations of compound **38** via an X-ray structure. A sample of the solid (c. 15 mg) was crystallized using slow vapor diffusion of hexanes into CH_2Cl_2. For full details of this X-ray structure, including the .cif file, please see the supporting information to a preliminary communication of this work.[45]



[45] Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678.

47

Internal alkyne 47: To a cooled flame-dried 50 mL round-bottomed flask was added terminal alkyne **22** (600 mg, 1.58 mmol). The flask was pumped down under high vacuum and backfilled with argon, and this procedure was repeated once. Dry THF (16 mL) was then added, and the solution was cooled to -78 °C. A 2.5 M solution of nBuLi in hexanes (710 μL, 1.77 mmol) was added slowly, dropwise. As equivalence was approached, the solution turned from a very pale yellow to a slightly deeper yellow. Within one minute after the addition of the last drop of nBuLi, the solution changed color more dramatically to a deeper orange. The authors advise that nBuLi addition proceed very gradually towards the end, as any excess equivalents of nBuLi result in a proportionate amount of decomposition. nBuLi addition should end immediately upon evolution of an orange color. After nBuLi addition, the solution was warmed for 5 min. by removing it from the -78 °C bath, during which time it developed an orange-brown color. After recooling to -78 °C, MeI (490 μL, 7.9 mmol) was added dropwise, over 2 min. The reaction was allowed to warm gradually to room temperature over 14 h., at which point it was quenched with sat. $NaHCO_3$ (15 mL) and diluted with Et_2O (20 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. The nearly pure crude oil was pulled through a short pad of SiO_2 (10% EtOAc in hexanes) to yield internal alkyne **47** as a colorless oil (615 mg, 1.56 mmol, 99%): R_f = 0.45 (10% EtOAc in hexanes).

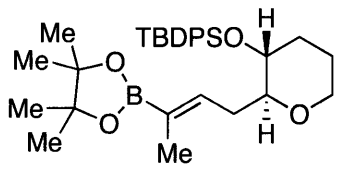
$[\alpha]^{22}_D$ = -17.0 (*c* = 2.6, $CDCl_3$).

IR (thin film, NaCl) 3072, 2932, 2857, 1590, 1472, 1428, 1362, 1099, 1047 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.74-7.68 (m, 4H), 7.47-7.42 (m, 2H), 7.39 (app t, *J* = 7.4 Hz, 4 H), 3.90-3.85 (m, 1H), 3.59-3.53 (m, 1H), 3.36-3.30 (m, 1H), 3.28 (ddd, *J* = 9.3, 6.5, 3.1 Hz, 1H), 2.70 (app dp, *J* = 16.8, 2.6 Hz, 1H), 2.47 (ddq, *J* = 16.8, 6.8, 2.6 Hz, 1H), 1.79 (app t, *J* = 2.6 Hz, 3H), 1.77-1.70 (m, 1H), 1.47-1.37 (m, 3H), 1.05 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 136.1, 134.9, 133.5, 129.9, 129.7, 127.8, 127.6, 81.2, 77.1, 76.0, 71.3, 68.2, 33.3, 27.1, 25.5, 22.8, 19.5, 4.1.

HR-MS (ESI) *m/z* calcd for $C_{25}H_{32}O_2Si$ $(M+Na)^+$: 415.2064, found 415.2065.



48

Alkenyl boronate ester 48: Internal alkyne **47** (616 mg, 1.56 mmol) was added to a dry, cooled sealed tube. The tube was pumped under high vacuum and then backfilled with argon, and this cycle repeated two times more. Pinacolborane (287 μL, 253 mg, 1.98 mmol) was added, followed by Et_3N (22 μL, 16 mg, 0.16 mmol) and Schwartz's reagent (41 mg, 0.16 mmol). The resulting beige slurry was heated to 60 °C and stirred vigorously for 28 h. while protected from light. On heating, the solid dissolves to afford a clear orange solution. After cooling, the crude reaction mixture was filtered through a short pad of SiO_2 (100% Et_2O) and concentrated *in vacuo* to a very pale yellow heavy oil containing a 2:1 mixture of pinacolate **48** (R_f = 0.36, 10% EtOAc in hexanes) and its regioisomer **48b** (R_f = 0.38, 10% EtOAc in hexanes), along with unreacted **47**, traces of a proton quench product, and borate and other impurities. These were separated via careful column chromatography (gradient 3% to 5% EtOAc in hexanes) to afford **48** (235 mg, 0.45 mmol, 29% (39% based on recovered **47**) in >20:1 regioisomeric purity along with unreacted **47** (163 mg, 26%).

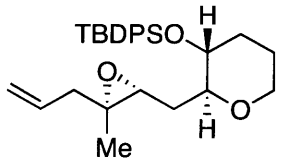
$[\alpha]^{22}_D$ = -2.1 (*c* = 1.9, $CDCl_3$).

IR (thin film, NaCl) 3072, 2932, 2246, 1632, 1472, 1428, 1371, 1301, 1103 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.71-7.67 (m, 4H), 7.45-7.36 (m, 6H), 6.43 (app tq, *J* = 6.4, 1.5 Hz, 1H), 3.81-3.76 (m, 1H), 3.45-3.39 (m, 1H), 3.30-3.24 (m, 2H), 2.81-2.75 (m, 1H), 2.08-2.00 (m, 1H), 1.82-1.77 (m, 1H), 1.63 (d, *J* = 1.5 Hz, 3H), 1.49-1.38 (m, 3H), 1.27 (app s, 12H), 1.04 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.43, 136.1, 136.1, 134.9, 133.9, 129.9, 129.7, 127.9, 127.6, 83.3, 82.4, 72.6, 67.9, 33.6, 32.1, 27.2, 25.8, 25.1, 25.0, 19.5, 14.5. (No signal was observed for the boron-bound carbon.)

HR-MS (ESI) *m/z* calcd for $C_{31}H_{46}BO_4Si$ $(M+Na)^+$: 543.3089, found 543.3089.



49

Epoxy alkene 49: [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) ($PdCl_2$(dppf)) (35 mg, 0.048 mmol) was added to a flame-dried, cooled sealed tube. Oven-dried potassium phosphate (1.53 g, 7.2 mmol) was added, and the tube was pumped on vacuum and backfilled with argon. This cycle was repeated two further times, and then alkenyl boronate ester **48** (500 mg, 0.96 mmol) was added as a solution in dry THF (1.5 mL). The mixture was allowed to stir under Ar for 5 min. to afford a

heterogeneous orange solution. Degassed water (35 mg, 35 μL, 1.9 mmol, degassed via sparging) was then added, followed immediately by allyl bromide (581 mg, 415 μL, 4.8 mmol). The sealed tub was capped, and the mixture was heated to 80 °C and stirred vigorously for 44 h., at which point it had become a chunky, pale yellow slurry. After cooling and dilution with Et_2O (5 mL), the crude product was filtered through SiO_2 (washed with Et_2O) and concentrated *in vacuo* to yield the crude 1,4-diene as a yellow oil (R_f = 0.60, 10% EtOAc in hexanes). This material was carried forward into Shi epoxidation without further purification.

To this crude diene in 2:1 v/v DMM:MeCN (14.2 mL) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} Na_2EDTA (9.5 mL), nBu$_4HSO_4$ (64 mg, 0.19 mmol), and chiral ketone **25** (248 mg, 0.96 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 25 min. via syringe pump, a solution of Oxone (652 mg, 1.06 mmol) in 4 x 10^{-4} Na_2EDTA (4.75 mL) and a 0.89 M solution of K_2CO_3 (4.75 mL, 4.22 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 30 min., at which point it was diluted with EtOAc (20 mL). The aqueous layer was separated and extracted with EtOAc (3x50 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. NMR and TLC evidence indicated ~90% conversion of the starting material. The desired trisubstituted epoxide **49** (R_f = 0.31 (10% EtOAc in hexanes)) was separated from unreacted diene via column chromatography (gradient 5% to 10% EtOAc in hexanes) to afford recovered diene (35 mg, 0.08 mmol, 8%) and epoxy alkene **49** (230 mg of an inseparable 3:1 diastereomeric mixture, 0.51 mmol, 53% over 2 steps (58% based on recovered starting material)). A small portion of **49** was purified further via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.5% *i*PrOH in hexanes, 20 mL/min.; t_R of desired diastereomer = 5.8 min.): R_f = 0.31 (10% EtOAc in hexanes).

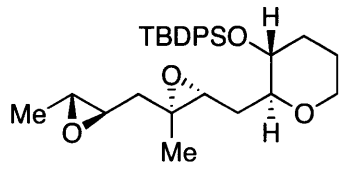
$[\alpha]^{22}_D$ of desired diastereomer in >20:1 dr = -25.6 (*c* = 0.60, $CDCl_3$).

IR (thin film, NaCl) 3072, 2931, 2857, 1473, 1428, 1382, 1100 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.65 (m, 4H), 7.46-7.41 (m, 2H), 7.41-7.36 (m, 4H), 5.80 (dddd, *J* = 17.2, 10.3, 7.0, 7.0 Hz, 1H), 5.14-5.07 (m, 2H), 3.86-3.80 (m, 1H), 3.46-3.40 (m, 1H), 3.33-3.24 (m, 2H), 2.93 (app t, *J* = 6.1 Hz, 1H), 2.35 (app dd, *J* = 14.2, 7.3 Hz, 1H), 2.18 (app dd, *J* = 14.2, 6.7 Hz, 1H), 2.10 (ddd, *J* = 14.4, 6.2, 2.7 Hz, 1H), 1.86-1.76 (m, 1H), 1.61-1.39 (m, 4H), 1.24 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.7, 134.0, 133.6, 130.0, 129.8, 127.9, 127.6, 117.8, 81.6, 72.5, 67.9, 60.9, 59.5, 43.4, 33.5, 32.0, 27.2, 25.6, 19.5, 16.9.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_3Si$ $(M+Na)^+$: 473.2482, found 473.2485.



51

Diepoxide 51: To a solution of Grubbs-Hoveyda 2nd generation catalyst **50** (23 mg, 0.037 mmol) in CH_2Cl_2 (3 mL) at -78 °C was added condensed *cis*-2-butene (approx. 3 mL, approx. 1.9 g, approx. 33 mmol). The resulting bright green solution was warmed to -15 °C, and epoxy alkene **49** (335 mg, 0.74 mmol, in 3:1 dr) was added dropwise as a solution in CH_2Cl_2 (7 mL) over 5 minutes. The reaction turned brown and then black over the course of the addition. After stirring for 5 additional min., a further portion of *cis*-2-butene was added (approx. 2 mL, approx. 1.2 g, approx. 22 mmol) and the reaction was stirred for 1.5 h. at -10 °C to -5 °C. The reaction was quenched at -15 °C with ethyl vinyl ether (10 mL, 7.5 g, 100 mmol), stirred 15 min., and then allowed to warm gradually to room temperature. After concentration *in vacuo* to yield a heavy black tar, the crude disubstituted alkene product was purified via filtration through a short pad of SiO_2 (10% EtOAc in hexanes) to afford an inseparable mixture of *E* and *Z* alkene isomers in ~4.2:1 *E*:*Z* stereoisomeric ratio, as a colorless oil (245 mg, 71%): R_f = 0.34 (10% EtOAc in hexanes). This mixture was carried forward without further purification.

To this crude mixture in 2:1 v/v DMM:MeCN (19.7 mL) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} Na_2EDTA (9.8 mL), nBu_4HSO_4 (44 mg, 0.13 mmol), and chiral ketone **25** (207 mg, 0.80 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 45 min. via syringe pump, a solution of Oxone (1.97 g, 3.2 mmol) in 4 x 10^{-4} Na_2EDTA (6.55 mL) and a 0.89 M solution of K_2CO_3 (6.55 mL, 5.83 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 30 min., at which point it was diluted with EtOAc (30 mL). The aqueous layer was separated and extracted with EtOAc (3x50 mL), and the combined organics were washed with brine, dried over Na_2SO_4, concentrated *in vacuo*, and chromatographed (15% EtOAc in hexanes) to provide diepoxide **51**, a colorless oil, as an inseparable mixture of diastereomers (220 mg of a 1.5:1 overall diastereomeric mixture, 0.46 mmol combined, 86%): R_f = 0.37 (20% EtOAc in hexanes). Diepoxide **51** was further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.4% *i*PrOH in hexanes, 30 mL/min.; t_R of desired diastereomer = 13.5 min.) to afford **51** in 7.5:1 to 10:1 overall dr (depending on the batch).

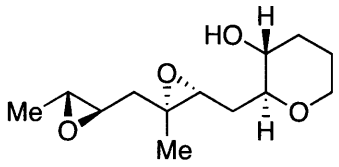
$[\alpha]^{22}_D$ of a 9:1 mixture = -2.5 (*c* = 4.6, $CDCl_3$).

IR (thin film, NaCl) 2932, 2857, 1589, 1473, 1428, 1382, 1362, 1101 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H), 7.46-7.36 (m, 6H), 3.86-3.81 (m, 1H), 3.43 (app td, *J* = 8.8, 4.5 Hz, 1H), 3.33-3.27 (m, 2H), 2.91 (app t, *J* = 6.1 Hz, 1H), 2.80-2.75 (m, 2H), 2.12 (ddd, *J* = 14.4, 6.2, 2.7 Hz, 1H), 1.86-1.79 (m, 1H), 1.77-1.65 (m, 2H), 1.58 (ddd, *J* = 14.6, 9.4, 6.0 Hz, 1H), 1.51-1.40 (m, 3H), 1.34-1.31 (m, 6H), 1.04 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 136.1, 134.6, 133.5, 130.0, 129.8, 127.9, 127.6, 81.4, 72.5, 67.9, 61.3, 58.4, 56.7, 54.3, 41.6, 33.4, 31.8, 27.2, 25.6, 19.5, 17.7, 17.3.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{40}O_4Si$ $(M+Na)^+$: 503.2588, found 503.2600.



44

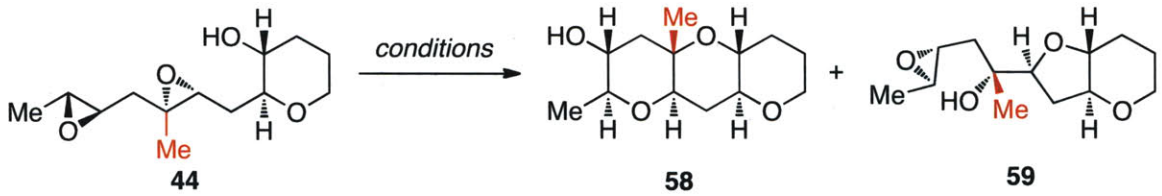
Diepoxy alcohol 44: To a solution of silyl ether **51** (113 mg, 0.24 mmol, in 7.5:1 overall dr) in THF (1 mL) was added a 1 M solution of TBAF in THF (470 μL, 0.47 mmol). The reaction was warmed to 30 °C for 2 h., cooled, and filtered through a pad of SiO_2 (gradient 20% to 50% to 100% EtOAc in hexanes) to yield free diepoxy alcohol **44** as a colorless oil (54 mg, 0.22 mmol, 95%): R_f = 0.55 (100% EtOAc); $[\alpha]^{22}_D$ of a 9:1 mixture of diastereomers = +25.0 (*c* = 2.0, $CDCl_3$). This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize traces of DCl in $CDCl_3$ with K_2CO_3 before collecting NMR data. **44** cyclizes very slowly on standing at -20 °C in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -20 °C as a neat oil. For extended periods, **44** is best stored frozen in benzene at -20 °C.

IR (thin film, NaCl) 3431, 2932, 2855, 1441, 1384, 1272, 1096 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95-3.89 (m,1H), 3.55-3.47 (m, 1H), 3.35 (app td, *J* = 11.3, 4.0 Hz, 1 H), 3.22 (ddd, *J* = 9.3, 6.1, 3.4 Hz, 1H), 3.04 (dd, *J* = 8.2, 3.7 Hz, 1H), 2.80-2.73 (m, 2H), 2.37 (d, *J* = 4.1 Hz, 1H), 2.14-2.05 (m, 2H), 1.82-1.74 (m, 2H), 1.74-1.61 (m, 3H), 1.47-1.34 (m, 4H), 1.30 (d, *J* = 5.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 81.0, 69.8, 68.1, 60.6, 59.1, 56.5, 54.4, 41.6, 32.6, 31.5, 25.9, 17.6, 17.2.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1413.

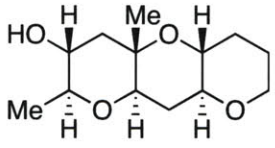


Reaction of diepoxy alcohol 44 to THP triad 58 and 6,5-fused 59:

Reaction in **water**: Diepoxy alcohol **44** (14.5 mg, 0.060 mmol, in 9:1 dr) was dissolved in deionized water (3.0 mL) in a 20 mL vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60 °C under air for 3 d. The solution was then cooled to rt and concentrated *in vacuo* (10 torr, 40 °C). The crude product mixture was chromatographed (30% EtOAc in hexanes) to separate the desired tris-THP **58** (8.0 mg, 0.033 mmol, 55% (61% adjusted for 9:1 dr), a white solid) from 6,5-fused side product **59** (4.1 mg, 0.017 mmol, 28%).

Reaction promoted by **CSA**: To a solution of diepoxy alcohol **44** (9.8 mg, 0.040 mmol, in 7.5:1 dr) in CH_2Cl_2 (2.0 mL) was added (+/-)-CSA (9.4 mg, 0.040 mmol) and stirred at rt under argon for 4 h. At this point the crude product mixture was diluted with CH_2Cl_2 (5 mL) and transferred to a separatory funnel. The reaction flask was washed out with EtOAc (3x6 mL) and H_2O (3x3 mL), and these combined washes were added to the separatory funnel. The organic layer was washed with sat. $NaHCO_3$ (2 mL), and the combined aqueous layers were extracted with EtOAc (3x40 mL). The combined organics were concentrated *in vacuo* without drying, and the crude product mixture was chromatographed (30% EtOAc in hexanes) to afford the desired tris-THP **58** (4.3 mg, 0.018 mmol, 44% (50% adjusted for 7.5:1 dr), a white solid).

Reaction promoted by **BF_3**: To a solution of diepoxy alcohol **44** (10.8 mg, 0.045 mmol, in 7.5:1 dr) in CH_2Cl_2 (2.24 mL) cooled to -78 °C was added, dropwise, a stock solution of 0.1 M BF_3•OEt_2 in CH_2Cl_2 (111 μL, 0.0011 mmol) and stirred at -78 °C under argon for 30 min. At this point the reaction was allowed to warm gradually to rt over 5 min., diluted with CH_2Cl_2 (5 mL), and quenched with sat. $NaHCO_3$ (800 μL). The resulting biphasic mixture was transferred to a separatory funnel. The reaction flask was washed out with EtOAc (3x6 mL) and H_2O (3x3 mL), and these combined washes were added to the separatory funnel. The aqueous layer was separated and extracted with EtOAc (3x40 mL), and the combined organics were concentrated *in vacuo* without drying. The crude product mixture was chromatographed (30% EtOAc in hexanes) to afford the desired tris-THP **58** (6.3 mg, 0.026 mmol, 58% (66% adjusted for 7.5:1 dr), a white solid).



58

tris-THP 58: $R_f = 0.51$ (100% EtOAc).

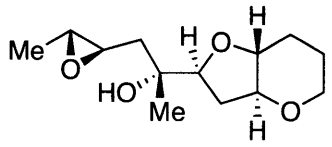
$[\alpha]^{22}_D = +16.1$ ($c = 0.38$, $CDCl_3$).

IR (thin film, NaCl) 3466, 2971, 2947, 2862, 1371, 1266, 1131, 1096, 1070, 1050, 1032, 947 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.96-3.90 (m, 1H), 3.53-3.45 (m, 1H), 3.43-3.35 (m, 2H), 3.27 (dq, J = 9.2, 6.1 Hz, 1H), 3.20 (dd, J = 12.3, 3.9 Hz, 1H), 3.02 (ddd, J = 11.4, 9.3, 4.5 Hz, 1H), 2.21 (dd, J = 11.6, 5.1 Hz, 1H), 2.11 (app td, J = 11.4, 4.2 Hz, 1H), 2.01-1.94 (m, 1H), 1.82-1.70 (m, 2H), 1.64 (app q, J = 11.7 Hz, 1H), 1.52-1.38 (m, 3H), 1.33 (d, J = 6.1 Hz, 3H), 1.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 80.1, 79.3, 78.9, 73.7, 71.6, 70.5, 68.4, 47.0, 31.3, 30.0, 26.0, 18.4, 16.2.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1421.



59

6,5-fused 59: $R_f = 0.45$ (100% EtOAc).

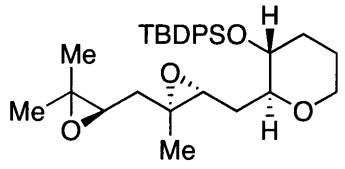
$[\alpha]^{22}_D = +19.1$ ($c = 0.14$, $CDCl_3$).

IR (thin film, NaCl) 3451, 2925, 2853, 1738, 1452, 1381, 1250, 1126, 1081, 966 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 4.05-3.97 (m, 2H), 3.47 (app td, J = 11.9, 3.1 Hz, 1H), 3.30-3.22 (m, 2H), 2.90 (ddd, J = 8.0, 3.3, 2.4 Hz, 1H), 2.77 (qd, J = 5.2, 2.3 Hz, 1H), 2.25-2.09 (m, 3H), 1.97-1.87 (m, 2H), 1.76-1.46 (m, 4H), 1.34 (s, 3H), 1.32 (d, J = 5.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 82.9, 81.4, 79.1, 74.3, 68.9, 56.2, 54.3, 39.6, 30.8, 30.0, 24.7, 24.0, 17.7.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1438.



53

Diepoxide 53: [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) ($PdCl_2$(dppf)) (73 mg, 0.10 mmol) was added to a flame-dried, cooled sealed tube. Oven-dried potassium phosphate (1.83 g, 8.63 mmol) was added, and the tube was pumped on vacuum and backfilled with argon. This cycle was repeated two further times, and then alkenyl boronate **48** (600 mg, 1.15 mmol) was added as a solution in dry THF (2 mL). The mixture was allowed to stir under Ar for 5 min. to afford a heterogeneous orange solution. Degassed water (42 mg, 42 μL, 2.3 mmol, degassed via sparging) was then added, followed immediately by prenyl bromide (859 mg, 666 μL, 5.76 mmol). The sealed tub was capped, and the mixture was heated to 80 °C and stirred vigorously for 42 h., at which point it had become a chunky, pale yellow slurry. After cooling and dilution with Et_2O (5 mL), the crude product was filtered through SiO_2 (washed with Et_2O) and concentrated *in vacuo* to yield a mixture of the desired S_N2 product **52** as well as undesired S_N2' product **52b**, as a yellow oil. These inseparable skipped diene isomers were purified away from phosphine and other impurities via column chromatography (gradient 2% to 3% EtOAc in hexanes) to give a 2.5:1 (S_N2:S_N2') mixture of diene isomers **52** (400 mg, 0.86 mmol, 75% combined yield, R_f = 0.63, 10% EtOAc in hexanes). This mixture was carried forward into Shi epoxidation without further purification.

To a solution of these dienes (400 mg, 0.86 mmol) in 2:1 v/v DMM:MeCN (23.2 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4 x 10^{-4} Na_2EDTA (15.5 mL), $n$$Bu_4HSO_4$ (75 mg, 0.22 mmol), and chiral ketone **25** (222 mg, 0.86 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 30 min. via syringe pump, a solution of Oxone (1.06 g, 1.73 mmol) in 4 x 10^{-4} Na_2EDTA (7.75 mL) and a 0.89 M solution of K_2CO_3 (7.75 mL, 6.9 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 20 min., at which point it was diluted with EtOAc (25 mL). The aqueous layer was extracted with EtOAc (3 x 25 mL), and the combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* to provide desired diepoxide **53** and diastereomers. The undesired S_N2' cross-coupling product **52b** formed in the previous step, which contains a monosubstituted alkene, is only partially oxidized under these conditions, to monoepoxide **54** (R_f = 0.77, 20% EtOAc in hexanes), which is readily separable from the desired diepoxide **53**. Column chromatography (15% EtOAc in hexanes) afforded diepoxide **53** in 3.5:1 overall dr as a colorless oil (276 mg, 0.56 mmol, 65% (49% yield over 2 steps), R_f = 0.54 (20% EtOAc in hexanes)) contaminated with a small quantity of ketone **25**. Diepoxide **53** was further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI 20 mm achiral SiO_2 column, 5 μm particle size; 99.5:0.5 hexanes:iPrOH, 20 mL/min.; t_R of desired diastereomer = 11.9 min.) to afford **53** free of **25** and in 15:1 to 20:1 overall dr (depending on batch).

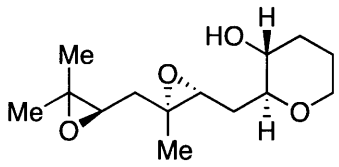
$[\alpha]^{22}_D$ for a sample in 20:1 dr = -7.5 (c = 3.3, $CDCl_3$).

IR (thin film, NaCl) 3072, 2958, 2930, 2857, 1590, 1472, 1462, 1428, 1379, 1102 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H), 7.46-7.41 (m, 2H), 7.40-7.36 (m, 4H), 3.85-3.80 (m, 1H), 3.43 (ddd, J = 9.3, 4.8, 4.5 Hz, 1H), 3.29 (app td, J = 9.3, 2.5 Hz, 1H), 2.93 (app t, J = 6.1 Hz, 1H), 2.89 (app t, J = 6.0 Hz, 1H), 2.11 (ddd, J = 14.4, 6.4, 2.7 Hz, 1H), 1.85-1.80 (m, 1H), 1.77-1.73 (m, 2H), 1.60 (ddd, J = 14.9, 9.5, 5.8 Hz, 1H), 1.51-1.39 (m, 3H), 1.33 (app s, 6H), 1.27 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.7, 133.6, 130.0, 129.8, 127.9, 127.7, 81.4, 72.5, 67.9, 61.3, 61.2, 58.8, 58.0, 38.2, 33.5, 31.8, 27.2, 25.6, 24.9, 19.5, 19.0, 17.3.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{42}O_4Si$ $(M+Na)^+$: 517.2745, found 517.2751.



45

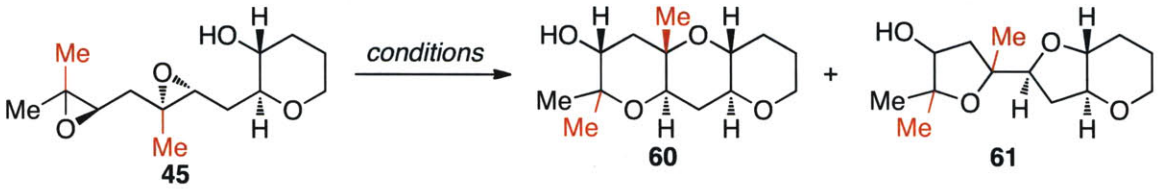
Diepoxy alcohol 45: To a solution of silyl ether **53** (64 mg, 0.13 mmol, in 20:1 overall dr) in dry THF (2 mL) was added a 1 M THF solution of TBAF (520 μL, 0.52 mmol). The reaction was warmed to 40 °C and stirred for 2 h. After cooling, the crude product was pulled directly through a SiO_2 plug (gradient 20% to 50% EtOAc in hexanes) and concentrated *in vacuo* to afford diepoxy alcohol **45** as a pale yellow oil (31 mg, 0.12 mmol, 92%): R_f = 0.58 (100% EtOAc); $[\alpha]^{22}_D$ = +17.8 (c = 2.0, $CDCl_3$). This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize traces of DCl in $CDCl_3$ with K_2CO_3 before collecting NMR data. **45** cyclizes very slowly on standing at -20 °C in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -20 °C as a neat oil. For extended periods, **45** is best stored frozen in benzene at -20 °C.

IR (thin film, NaCl) 3439, 2928, 2854, 1459, 1379, 1251, 1096, 1043 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.94-3.89 (m, 1H), 3.51 (ddd, J = 10.9, 9.2, 4.5 Hz, 1H), 3.38-3.32 (m, 1H), 3.22 (ddd, J = 9.3, 6.1, 3.4 Hz, 1H), 3.06 (dd, J = 8.0, 3.9 Hz, 1H), 2.89 (dd, J = 7.2, 4.8 Hz, 1H), 2.41 (broad s, 1H), 2.14-2.05 (m, 2H), 1.84-1.77 (m, 2H), 1.74-1.65 (m, 3H), 1.47-1.38 (m, 1H), 1.38 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 81.0, 69.9, 68.1, 61.1, 60.7, 59.4, 58.1, 38.3, 32.6, 31.5, 25.9, 24.9, 19.0, 17.2.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_4$ $(M+Na)^+$: 279.1567, found 279.1566.

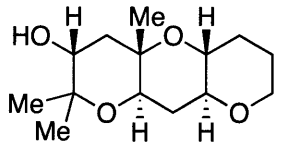


Reaction of diepoxy alcohol 45 to THP triad 60 and 6,5-fused 61:

Reaction in **water**: Diepoxy alcohol **45** (13.7 mg, 0.053 mmol, in 15:1 dr) was dissolved in deionized water (2.7 mL) in a 20 mL vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60 °C under air for 3 d. The solution was then cooled to rt and concentrated *in vacuo* (10 torr, 40 °C). The crude product mixture was chromatographed (50% EtOAc in hexanes) to separate the desired tris-THP **60** (6.9 mg, 0.027 mmol, 50% (54% adjusted for 15:1 dr), a white solid) from 6,5-fused side product **61** (5.4 mg, 0.021 mmol, 39%).

Reaction promoted by **CSA**: To a solution of diepoxy alcohol **45** (13.1 mg, 0.051 mmol, in 20:1 dr) in CH_2Cl_2 (2.5 mL) was added (+/-)-CSA (11.8 mg, 0.051 mmol) and stirred at rt under argon for 4 h. At this point the crude product mixture was diluted with CH_2Cl_2 (5 mL) and transferred to a separatory funnel. The reaction flask was washed out with EtOAc (3x6 mL) and H_2O (3x3 mL), and these combined washes were added to the separatory funnel. The organic layer was washed with sat. $NaHCO_3$ (2 mL), and the combined aqueous layers were extracted with EtOAc (3x40 mL). The combined organics were concentrated *in vacuo* without drying, and the crude product mixture was chromatographed (50% EtOAc in hexanes) to afford the desired tris-THP **60** (3.5 mg, 0.018 mmol, 27% (29% adjusted for 20:1 dr), a white solid).

Reaction promoted by **BF_3**: To a solution of diepoxy alcohol **45** (15.1 mg, 0.059 mmol, in 15:1 dr) in CH_2Cl_2 (3.0 mL) cooled to -78 °C was added, dropwise, a stock solution of 0.1 M BF_3•OEt_2 in CH_2Cl_2 (147 μL, 0.015 mmol) and stirred at -78 °C under argon for 30 min. At this point the reaction was allowed to warm gradually to rt over 5 min., diluted with CH_2Cl_2 (5 mL), and quenched with sat. $NaHCO_3$ (800 μL). The resulting biphasic mixture was transferred to a separatory funnel. The reaction flask was washed out with EtOAc (3x6 mL) and H_2O (3x3 mL), and these combined washes were added to the separatory funnel. The aqueous layer was separated and extracted with EtOAc (3x40 mL), and the combined organics were concentrated *in vacuo* without drying. The crude product mixture was chromatographed (50% EtOAc in hexanes) to afford the desired tris-THP **60** (8.0 mg, 0.031 mmol, 53% (57% adjusted for 15:1 dr), a white solid) along with 6,5-fused side product **61** (3.8 mg, 0.015 mmol, 25%).



60

THP triad 60: R_f = 0.61 (100% EtOAc).

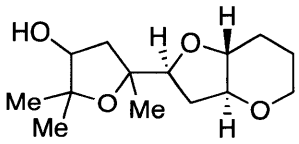
$[\alpha]^{22}_D$ = +54.8 (*c* = 1.0, $CDCl_3$).

IR (thin film, NaCl) 3449, 2968, 2934, 2877, 1419, 1379, 1354, 1268, 1218, 1128, 1097, 1069, 1026, 949, 940 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.95-3.89 (m, 1H), 3.66 (dd, *J* = 11.7, 4.6 Hz, 1H), 3.42-3.34 (m, 3H), 3.03 (ddd, *J* = 11.3, 9.3, 4.5 Hz, 1H), 2.01-1.93 (m, 3H), 1.81-1.68 (m, 2H), 1.64-1.54 (m, 3H), 1.42 (ddd, *J* = 11.9, 11.9, 5.3 Hz, 1H), 1.31 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 79.2, 76.8, 74.3, 73.1, 71.7, 70.5, 68.5, 43.4, 31.5, 30.0, 28.4, 26.0, 17.0, 15.6.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_4$ $(M+Na)^+$: 279.1567, found 279.1574.



61

6,5-fused 61: R_f = 0.56 (100% EtOAc).

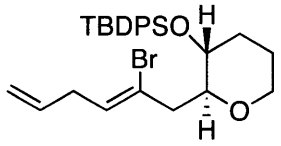
$[\alpha]^{22}_D$ = -41.7 (*c* = 0.48, $CHCl_3$).

IR (thin film, NaCl) 3366, 2964, 2935, 2850, 1453, 1371, 1277, 1141, 1117, 1068, 1059, 1040, 1021, 974 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 4.76 (d, *J* = 11.8 Hz, 1H), 4.05 (dd, *J* = 10.9, 5.9 Hz, 1H), 4.01-3.96 (m, 1H), 3.82 (dd, *J* = 11.7, 5.3 Hz, 1H), 3.50-3.38 (m, 2H), 3.29 (ddd, *J* = 11.2, 9.1, 5.9 Hz, 1H), 2.29-2.17 (m, 3H), 2.11 (d, *J* = 14.5 Hz, 1H), 1.75-1.52 (m, 4H), 1.30 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 85.3, 85.0, 83.2, 80.3, 79.5, 78.1, 68.9, 40.9, 33.6, 29.7, 27.8, 26.8, 24.6, 23.2.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_4$ $(M+Na)^+$: 279.1567, found 279.1571.



55

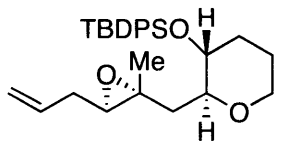
Alkenyl bromide 55: To $PdCl_2(PhCN)_2$ (40 mg, 0.11 mmol) and $NaHCO_3$ (880 mg, 10.5 mmol) was added allyl bromide (9 mL, 105 mmol). The resulting solution was stirred 15 minutes at room temperature, over which time the color changed from an initial yellow-orange to a deeper red-brown. Alkyne **22** (795 mg, 2.1 mmol) as a solution in THF (2 mL) was then added dropwise at ambient temperature via syringe pump over 90 min. After addition the reaction was stirred a further 30 min., directly concentrated *in vacuo*, and chromatographed (gradient 2% to 3% to 5% EtOAc in hexanes) to afford alkenyl bromide **55** (920 mg, 1.84 mmol, 88%): R_f = 0.54 (10% EtOAc in hexanes); $[\alpha]^{22}_D$ = -11.5 (*c* = 27.0, $CDCl_3$). We have found that the presence of silanol impurities (ie *t*-butyldiphenylsilanol, TBDPSOH) in starting material **22** does not adversely affect the bromoallylation reaction, and, in fact, purification away from TBDPSOH is easier after this step than after the synthesis of **55**.

IR (thin film, NaCl) 3072, 3011, 2933, 2858, 1639, 1472, 1428, 1362, 1218, 1127, 1103, 1048 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (app t, *J* = 8.4 Hz, 4H), 7.56-7.46 (m, 6H), 5.92 (dddd, *J* = 16.5, 10.1, 6.2, 6.2 Hz, 1H), 5.85 (app t, *J* = 6.8 Hz, 1H), 5.22 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.13 (dd, *J* = 10.1, 1.5 Hz, 1H), 3.92-3.87 (m, 1H), 3.71 (app td, *J* = 9.2, 1.5 Hz, 1H), 3.55 (ddd, *J* = 10.2, 9.1, 4.6 Hz, 1H), 3.39 (app td, *J* = 11.3, 2.7 Hz, 1H), 3.32 (app d, *J* = 14.7 Hz, 1H), 3.13-3.02 (m, 2H), 2.43 (dd, *J* = 14.8, 10.0 Hz, 1H), 2.05-2.00 (m, 1H), 1.70-1.62 (m, 1H), 1.60-1.48 (m, 2H), 1.23 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 135.9, 134.9, 134.3, 133.5, 129.9, 129.7, 127.8, 127.6, 126.0, 115.5, 80.0, 71.9, 67.6, 44.5, 35.8, 33.5, 27.1, 25.5, 19.3.

HR-MS (ESI) *m/z* calcd for $C_{27}H_{35}BrO_2Si$ $(M+Na)^+$: 521.1482, found 521.1489.



56

Epoxide 31: To a dried, cooled sealed tube was added $Pd(PPh_3)_4$ (218 mg, 0.19 mmol). The tube was pumped out under high vacuum and backfilled with argon three times. A 2.0 M solution of dimethylzinc in toluene (6.75 mL, 13.5 mmol) was then added to afford a lemon yellow solution, which was cooled to 0 °C. Alkenyl bromide **55** (1.35 g, 2.7 mmol) was then added gradually as a solution in THF (10 mL). The tube was then capped and heated to 85 °C for 48 h. After cooling, the reaction was quenched by pouring over a mixture of ~60 g of ice and ~20 g of NaCl. The aqueous layer was separated and extracted Et_2O (3x75 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude diene product, a vivid yellow-orange oil containing the desired methylated, trisubstituted alkene along with traces of triphenylphosphine and a proton-quenched, disubstituted alkene impurity, was carried forward without further purification (R_f of trisubstituted and disubstituted alkenes = 0.60 (10% EtOAc in hexanes)).

To this crude mixture in 2:1 v/v DMM:MeCN (34 mL) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} Na_2EDTA (23 mL), $n Bu_4HSO_4$ (153 mg, 0.45 mmol), and chiral ketone **25** (613 mg, 2.37 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 30 min. via syringe pump, a solution of Oxone (1.46 g, 2.37 mmol) in 4 x 10^{-4} Na_2EDTA (11.4 mL) and a 0.89 M solution of K_2CO_3 (11.4 mL, 10.2 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 20 min., at which point it was diluted with EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (3x120 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. NMR and TLC evidence indicated only partial conversion of starting material. This partially oxidized reaction mixture was then subjected again to identical epoxidation conditions and worked up as before. For reasons unknown, attempting to force full conversion in a single subjection by using greater than 1-1.05 equivalents of Oxone appears to lead to epoxidation of the disubstituted alkene side product as well, forming an undesired disubstituted epoxide side product difficult to remove from the desired product. The desired trisubstituted epoxide **56** (R_f = 0.39 (10% EtOAc in hexanes)) was partially separated from its undesired diastereomer (crude dr ≅ 2:1, R_f of undesired diastereomer = 0.45 (10% EtOAc in hexanes)) via column chromatography (gradient 2% to 3% to 5% to 10% EtOAc in hexanes) to afford epoxy alkene **56** (580 mg of a 4:1 diastereomeric mixture, 1.29 mmol combined, 48% over 2 steps (38% over 2 steps for desired diastereomer)).

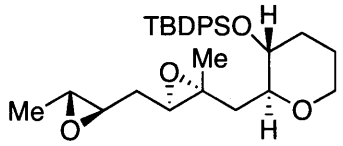
$[\alpha]^{22}_D$ of desired diastereomer in 20:1 dr = -9.4 (*c* = 0.19, $CDCl_3$).

IR (thin film, NaCl) 3070, 2931, 2857, 1471, 1428, 1100 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H), 7.46-7.41 (m, 2H), 7.41-7.36 (m, 4H), 5.88 (dddd, J = 16.8, 10.3, 6.4, 6.4 Hz, 1H), 5.17 (app dq, J = 17.3, 1.7 Hz, 1H), 5.11 (app dq, J = 10.3, 1.5 Hz, 1H), 3.81-3.76 (m, 1H), 3.35-3.22 (m, 3H), 2.84 (app t, J = 6.4 Hz, 1H), 2.38 (dddd, J = 15.3, 15.3, 1.4, 1.4 Hz, 1H), 2.30-2.22 (m, 2H), 1.85-1.79 (m, 1H), 1.50-1.38 (m, 4H), 1.30 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 136.1, 134.7, 134.2, 133.7, 130.0, 129.8, 127.9, 127.7, 117.0, 79.9, 72.1, 67.5, 61.0, 59.7, 40.3, 33.5, 33.3, 27.2, 25.6, 19.5, 17.9.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_3Si$ $(M+Na)^+$: 473.2482, found 473.2476.



57

Diepoxide 57: To a solution of Grubbs-Hoveyda 2nd generation catalyst **50** (80 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) at -78 °C was added condensed *cis*-2-butene (approx. 3.5 mL, approx. 2.2 g, approx. 39 mmol). The resulting bright green solution was warmed to -15 °C, and epoxy alkene **56** (580 mg, 1.29 mmol, in 4:1 dr) was added as a solution in CH_2Cl_2 (21 mL). The reaction turned brown and then black over the course of a few minutes. After stirring for 4 h., the reaction was quenched at -15 °C with ethyl vinyl ether (8 mL, 6 g, 84 mmol), stirred 15 min., and then allowed to warm gradually to room temperature. After concentration *in vacuo* to yield a heavy black tar, the crude product was purified via filtration through a short pad of SiO_2 (10% EtOAc in hexanes) to afford the crude disubstituted alkene product, a mixture of *E* and *Z* alkene isomers in ~4.1:1 *E*:*Z* stereoisomeric ratio, as a pale gray oil (600 mg, 99%): R_f = 0.39 (10% EtOAc in hexanes). This crude mixture was carried forward without further purification.

To this crude mixture in 2:1 v/v DMM:MeCN (48 mL) was added a 0.05 M solution of $Na_2B_4O_7$•$10H_2O$ in 4 x 10^{-4} Na_2EDTA (24 mL), $n$$Bu_4HSO_4$ (221 mg, 0.65 mmol), and chiral ketone **25** (503 mg, 1.95 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 45 min. via syringe pump, a solution of Oxone (4.8 g, 7.8 mmol) in 4 x 10^{-4} Na_2EDTA (16.1 mL) and a 0.89 M solution of K_2CO_3 (16.1 mL, 14.3 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 30 min., at which point it was diluted with EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (3x75 mL), and the combined organics were washed with brine, dried over Na_2SO_4, concentrated *in vacuo*, and chromatographed (15% EtOAc in hexanes) to achieve some separation of diepoxide diastereomers. Diepoxide **57**, a colorless oil, was obtained as a mixture of diastereomers (560 mg of a 2.7:1 overall diastereomeric mixture, 1.17 mmol combined, 90% (66% of desired diastereomer)): R_f = 0.36 (20% EtOAc in hexanes). The

diastereomeric enrichment of this mixture was determined by achiral analytical HPLC analysis (Supelco SUPELCOSIL LC-SI, 5 μm particle size, 25 cm length; 0.5% *i*PrOH in hexanes, 1.00 mL/min; t_R(major) = 12.14 min., t_R(minor) = 10.64 min., 13.13 min., 14.20 min.). Diepoxide **57** was further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.5% *i*PrOH in hexanes, 20 mL/min.; t_R of desired diastereomer = 10.6 min.) to afford **57** in 20:1 overall dr.

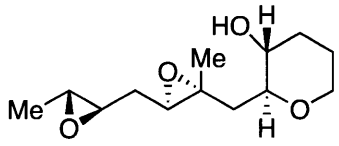
$[\alpha]^{22}_D$ = -1.4 (*c* = 6.6, $CDCl_3$).

IR (thin film, NaCl) 3071, 2932, 2858, 1473, 1428, 1381, 1102 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.70-7.65 (m, 4H), 7.46-7.36 (m, 6H), 3.82-3.77 (m, 1H), 3.35-3.24 (m, 3H), 2.92 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.87-2.82 (m, 2H), 2.27 (dd, *J* = 14.7, 1.2 Hz, 1H), 1.86-1.79 (m, 2H), 1.75 (ddd, *J* = 14.5, 7.6, 4.7 Hz, 1H), 1.50-1.36 (m, 4H), 1.34 (d, *J* = 4.9 Hz, 3H), 1.28 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.6, 133.7, 130.0, 129.8, 127.9, 127.6, 79.8, 72.2, 67.5, 59.6, 58.9, 57.3, 54.7, 40.3, 33.5, 32.0, 27.2, 25.6, 19.5, 18.0, 17.8.

HR-MS (ESI) *m/z* calcd for $C_{29}H_{40}O_4Si$ $(M+Na)^+$: 503.2588, found 503.2580.



46

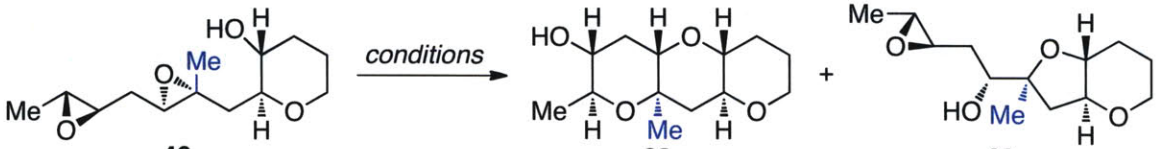
Diepoxy alcohol 46: To a solution of silyl ether **57** (130 mg, 0.27 mmol, in 20:1 overall dr) in THF (2 mL) was added a 1 M solution of TBAF in THF (540 μL, 0.54 mmol). The reaction was warmed to 40 °C for 3 h., cooled, and filtered through a pad of SiO_2 (gradient 20% to 50% to 100% EtOAc in hexanes) to yield free diepoxy alcohol **7** as a colorless oil (64 mg, 0.26 mmol, 98%): R_f = 0.49 (100% EtOAc); $[\alpha]^{22}_D$ = +29.0 (*c* = 1.55, $CDCl_3$). This material is highly sensitive to acid. Exposure to even traces of acid will induce cyclization. We found it essential to neutralize traces of DCl in $CDCl_3$ with K_2CO_3 before collecting NMR data. Diepoxy alcohol **46** cyclizes very slowly on standing at -20 °C in aprotic organic solvents (CH_2Cl_2 or EtOAc/hexanes) and somewhat faster on standing at -20 °C as a neat oil. For extended periods, **46** is best stored frozen in benzene at -20 °C.

IR (thin film, NaCl) 3429, 2924, 2852, 1443, 1382, 1094 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93-3.88 (m, 1H), 3.46-3.38 (m, 1H), 3.33-3.27 (m, 1H), 3.14 (ddd, J = 9.6, 7.3, 2.8 Hz, 1H), 2.99 (dd, J = 7.3, 5.1 Hz, 1H), 2.86-2.81 (m, 2H), 2.48 (d, J = 4.7 Hz, 1H), 2.16 (dd, J = 15.1, 2.8 Hz, 1H), 2.14-2.08 (m, 1H), 1.84-1.64 (m, 5H), 1.44-1.34 (m, 4H), 1.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 80.3, 69.9, 68.0, 60.0, 60.0, 57.1, 54.8, 40.6, 32.7, 31.8, 25.9, 17.9, 17.7.

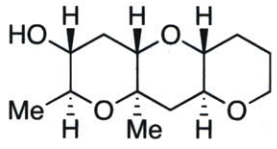
HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1406.



46 62 63

Reaction of diepoxde 46 to THP triad 62 and 6,5-fused 63:

Reaction in **water**: Diepoxy alcohol **46** (15.0 mg, 0.062 mmol, in 20:1 dr) was dissolved in deionized water (3.1 mL) in a 20 mL vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60 °C under air for 3 d. The solution was then cooled to rt and concentrated *in vacuo* (10 torr, 40 °C). The crude product mixture was chromatographed (30% EtOAc in hexanes) to separate the desired tris-THP **62** (4.7 mg, 0.0194 mmol, 31% (33% adjusted for 20:1 dr), a white solid) from 6,5-fused side product **63** (4.4 mg, 0.0182 mmol, 29%).



62

THP diad 62: R_f = 0.51 (100% EtOAc).

$[\alpha]^{22}_D$ = -34.0 (c = 0.44, $CDCl_3$).

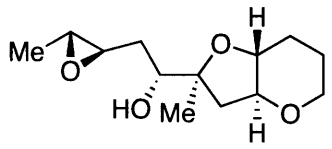
IR (thin film, NaCl) 3434, 2944, 2871, 1463, 1378, 1337, 1284, 1110, 1077, 1053, 1040, 1008 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96-3.91 (m, 1H), 3.55 (dq, J = 9.3, 6.0 Hz, 1H), 3.43-

3.31 (m, 2H), 3.22-3.09 (m, 3H), 2.16 (ddd, J = 11.6, 4.6, 4.3 Hz, 1H), 2.14-2.06 (m, 2H), 1.82-1.70 (m, 2H), 1.66-1.57 (m, 2H), 1.55-1.45 (m, 2H), 1.29 (s, 3H), 1.26 (d, J = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 80.3, 79.3, 77.6, 73.2, 72.8, 70.3, 68.4, 43.8, 34.0, 29.7, 25.9, 18.7, 16.2.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1416.



63

6,5-fused 63: R_f = 0.48 (100% EtOAc).

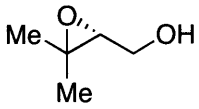
$[\alpha]^{22}_D$ = -8.9 (c = 0.065, $CDCl_3$).

IR (thin film, NaCl) 3417, 2956, 2921, 2863, 1465, 1373, 1119, 1104, 1063, 858 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02-3.97 (m, 1H), 3.79-3.74 (m, 1H), 3.47 (app td, J = 11.9, 3.2 Hz, 1H), 3.35 (ddd, J = 11.0, 9.0, 3.9 Hz, 1H), 3.28 (ddd, J = 11.0, 9.0, 6.4 Hz, 1H), 2.95 (ddd, J = 6.4, 4.0, 2.3 Hz, 1H), 2.91 (qd, J = 5.2, 2.3 Hz, 1H), 2.48 (d, J = 1.8 Hz, 1H), 2.24-2.18 (m, 1H), 2.10 (app t, J = 11.1 Hz, 1H), 1.83 (dd, J = 11.1, 6.4 Hz, 1H), 1.77-1.46 (m, 5H), 1.34 (d, J = 5.2 Hz, 3H), 1.21 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 83.7, 80.9, 79.8, 74.9, 69.0, 57.9, 55.1, 36.4, 33.8, 30.3, 25.1, 24.8, 17.8.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+Na)^+$: 265.1410, found 265.1415.



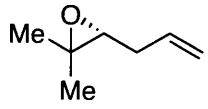
69

Epoxy alcohol 69: According to a procedure from Snider and coworkers[46], powdered 4

[46] Zou, Y.; Lobera, M.; Snider, B. B. *J. Org. Chem.* **2005**, *70*, 1761-1770, from supporting information.

Å molecular sieves (6.2 g) were flame dried and cooled in a 1 L round bottom flask. To this was added CH_2Cl_2 (350 mL) and D-(-)-DIPT (3.32 mL, 3.72 g, 15.8 mmol), and the resulting solution was cooled to -20 °C. To this solution was added $Ti(OiPr)_4$ (3.48 mL, 3.26 g, 11.4 mmol), and the resulting solution was stirred 10 min. at -20 °C. To this solution was added prenol (**68**, 6.00 mL, 5.08 g, 59 mmol), and the resulting solution was stirred 40 min. at -20 °C. To this solution was added a 5-6 M solution of TBHP in decane (24 mL, 120-144 mmol), and the resulting solution was stirred 19 h. at -20 °C. The reaction was quenched at -20 °C with 20 mL of a 40% NaOH solution in sat. aqueous NaCl (which was prepared from 8 g NaOH, 18 mL H_2O, and 1 g NaCl). Et_2O (40 mL) was added immediately thereafter, the cold bath was removed, and the mixture was allowed to stir for 20 min. At this point $MgSO_4$ (20 g) and Celite (2 g) were added, and the mixture was stirred a further 15 min. Stirring was stopped to allow the solids to settle, and then the solution was filtered through Celite. The Celite filter pad was washed repeatedly with CH_2Cl_2, and the combined organics were concentrated *in vacuo* and chromatographed (gradient 33% Et_2O in pentane to 100% Et_2O) to furnish epoxy alcohol **69** (5.2 g, 51 mmol, 87%): $R_f = 0.51$ (100% EtOAc), $[\alpha]^{22}_D = +18.5$ ($c = 2.0$, $CDCl_3$).

^1H and ^{13}C data were consistent with that reported by Snider and coworkers.[46]



70

Epoxy alkene 70: To a solution of PPh_3 (8.8 g, 33.6 mmol) and imidazole (2.4 g, 35 mmol) in a 3:1 mixture of Et_2O (105 mL) and MeCN (35 mL) at 0 °C was added I_2 (8.5 g, 33.6 mmol) gradually, portionwise, over 20 min. The resulting bright opaque yellow solution was warmed to rt for 15 min., then recooled to 0 °C, at which point epoxy alcohol **69** (2.66 g, 26 mmol) was added, dropwise, over 10 min. The resulting darker, browner solution was warmed to rt and stirred for 30 min. The reaction was then quenched with sat. $Na_2S_2O_3$ (20 mL). The organic layer was washed with sat. $NaHCO_3$ (100 mL). The combined aqueous layers were extracted with Et_2O (3x100 mL), and the combined organic layers were then washed with brine, dried over $MgSO_4$, concentrated *in vacuo* (BEWARE! The epoxy iodide. Concentration should be done at 40 torr/0 °C or at high pressure to avoid pumping off product!), and filtered through a short pad of SiO_2 (10% Et_2O in pentane) to afford the iodide (4.83 g, 22.8 mmol, 88%) as a thin, pale orange-pink solution in pentane/Et_2O: $R_f = 0.52$ (10% EtOAc in hexanes). Due to its instability, the epoxy iodide should be stored cold as a dilute solution in pentane/Et_2O and used quickly. A telltale sign of decomposition is the evolution of color from a pale orange-pink to a deep orange-red. The iodide was carried forward into the next step without further purification.

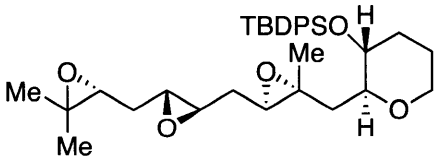
This vinylmetal displacement was adapted from the procedure of Nicolaou and coworkers.[39] To a flask containing CuBr•SMe_2 (180 mg, 0.94 mmol) was slowly added a solution of iodide **31** (1.0 g, 4.7 mmol) in Et_2O (4.7 mL). The resulting slurry was cooled to -23 °C and HMPA (3.3 mL, 3.4 g, 18.9 mmol) was added, to give a pale yellow slurry. To this was added, dropwise and with vigorous stirring, a 1.0 M solution of vinylmagnesium bromide in THF (9.4 mL, 9.4 mmol) over 15 min. With the addition of a small amount of Grignard reagent, the reaction solution changed color from yellow to yellow-brown to green-brown to black. After addition, the reaction was stirred 2 min. more and then diluted with Et_2O (10 mL) and quenched with sat. NH_4Cl (10 mL). The biphasic mixture was allowed to warm to rt, and the aqueous layer was extracted with pentane (2x10 mL) followed by Et_2O (2x10 mL). The combined organics were washed with sat. NaCl, dried over $MgSO_4$, and concentrated *in vacuo* (BEWARE! **70** is volatile. Concentration should be done at 40 torr/0 °C or at high pressure to avoid pumping off product!), and the crude product was purified by filtration through a short pad of SiO_2 (5% Et_2O in pentane) to afford epoxy alkene **70** (400 mg, 3.6 mmol, 76%) as a concentrated solution in pentane/Et_2O: R_f = 0.53 (10% EtOAc in hexanes).

$[\alpha]^{22}_D$ = +0.2 (*c* = 8.5, CD_2Cl_2).

IR (thin film, NaCl) 3584, 3081, 2962, 2927, 1642, 1459, 1379, 1326, 1250, 1122 cm^{-1}.

^1H NMR (500 MHz, CD_2Cl_2) δ 5.86 (dddd, *J* = 16.8, 10.3, 6.5, 6.5, 1H), 5.12 (app dq, *J* = 17.2, 1.7 Hz, 1H), 5.07 (app dq, *J* = 10.3, 1.5 Hz, 1H), 2.74 (app t, *J* = 6.4 Hz, 1H), 2.34-2.27 (m, 1H), 2.25-2.17 (m, 1H), 1.27 (s, 3H), 1.24 (s, 3H).

^{13}C NMR (100 MHz, CD_2Cl_2) δ 134.7, 117.0, 63.3, 58.4, 34.0, 25.1, 19.0.



71

Triepoxide 71: To a forest green solution of Hoveyda-Grubbs 2nd generation catalyst **50** (213 mg, 0.34 mmol) in CH_2Cl_2 (2 mL) was added epoxy alkene **56** (2.93 g, 6.5 mmol) as a solution in CH_2Cl_2 (30 mL), at which point the solution quickly turned black. Epoxy alkene **70** (1.8 g, 16 mmol) was subsequently added as a solution in ~5:1 pentane:Et_2O (20 mL). The reaction was stirred 16 h. at rt, at which an additional portion of Hoveyda-Grubbs 2nd generation catalyst **50** (213 mg, 0.34 mmol) was added. The reaction was stirred 24 h. more, at which point a final portion of Hoveyda-Grubbs 2nd generation catalyst **50** (213 mg, 0.34 mmol) was added. The reaction was stirred a final 30 h. and then quenched with ethyl vinyl ether (8 mL). The reaction mixture was concentrated *in vacuo* (BEWARE! **70** is volatile. Concentration should be done at 40 torr/0° or at high pressure to avoid pumping off **70**), to a heavy black tar and chromatographed (gradient

5% to 10% to 15% to 30% Et_2O in pentane) to recover unreacted starting materials **70** (200 mg, 11%) and **56** (960 mg, 33%). The column was then flushed with Et_2O. This flush was concentrated *in vacuo* and rechromatographed (gradient 20% to 50% EtOAc in hexanes) to furnish the diepoxy alkene as an inseparable mixture of alkene isomers in unknown *E*:*Z* ratio contaminated with homodimers of both **70** and **56**. This mixture (R_f = 0.39 (20% EtOAc in hexanes)) was carried forward into Shi epoxidation without further purification.

To this crude sample diepoxy alkene in 2:1 v/v DMM:MeCN (228 mL) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} Na_2EDTA (152 mL), $n$$Bu_4HSO_4$ (458 mg, 1.35 mmol), and chiral Shi ketone **25** (1.74 g, 6.75 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 1 h. via syringe pump, a solution of Oxone (16.6 g, 27 mmol) in 4 x 10^{-4} Na_2EDTA (76 mL) and a 0.89 M solution of K_2CO_3 (76 mL, 68 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 1 h., at which point it was diluted with EtOAc (200 mL). The aqueous layer was separated and extracted with EtOAc (3x300 mL), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. NMR and TLC analysis at this point indicated only partial conversion of starting material. This partially oxidized reaction mixture was then subjected again to identical epoxidation conditions and worked up as before to afford crude triepoxide **71** (610 mg, 1.11 mmol, 41%) in 2.5:1 overall dr. The diastereomeric enrichment of this mixture was determined by achiral analytical HPLC analysis (Supelco SUPELCOSIL LC-SI, 5 μm particle size, 25 cm length; 1.5% *i*PrOH in hexanes, 1.00 mL/min; t_R(major) = 11.48 min., t_R(minor) = 10.13 min., 10.50 min., 10.72 min., 12.51 min.). Triepoxide **71** was further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI 20 mm achiral SiO_2 column, 5 μm particle size; 98.0:2.0 hexanes:iPrOH, 20 mL/min.; t_R of desired diastereomer = 9.6 min.) to afford **71** in 10:1 to 20:1 dr: R_f = 0.42 (30% EtOAc in hexanes).

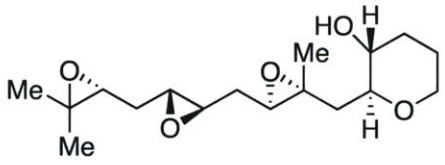
$[\alpha]^{22}_D$ = +13.7 (*c* = 0.4, $CDCl_3$).

IR (thin film, NaCl) 2958, 2931, 2857, 1461, 1428, 1379, 1102 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H), 7.46-7.41 (m, 2H), 7.41-7.36 (m, 4H), 3.82-3.77 (m, 1H), 3.35-3.24 (m, 3H), 2.98-2.91 (m, 4H), 2.28 (dd, *J* = 14.8, 1.5 Hz, 1H), 1.90 (ddd, *J* = 14.5, 7.2, 3.8 Hz, 1H), 1.84-1.79 (m, 3H), 1.70 (ddd, *J* = 14.5, 6.9, 5.3 Hz, 1H), 1.50-1.25 (m, 13H), 1.04 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.6, 133.7, 130.0, 129.8, 127.9, 127.7, 79.8, 72.2, 67.6, 61.1, 59.6, 58.8, 58.4, 56.2, 55.9, 40.2, 33.5, 32.3, 32.0, 27.2, 25.6, 24.9, 19.5, 19.0, 18.0.

HR-MS (ESI) *m/z* calcd for $C_{33}H_{46}O_5Si$ $(M+Na)^+$: 573.3007, found 573.3012.



67

67: To a solution of protected triepoxy alcohol **71** (255 mg, 0.46 mmol, 10:1 overall dr) in THF (3 mL) was added a 1 M solution of TBAF in THF (920 μL, 0.92 mmol). The reaction was warmed to 40 °C for 30 min., cooled, and filtered through a pad of SiO_2 (gradient 20% to 50% to 100% EtOAc in hexanes) to yield free triepoxy alcohol **71** as a very pale yellow oil (135 mg, 0.43 mmol, 93%): $R_f = 0.45$ (100% EtOAc).

$[\alpha]^{22}_D = +21.0$ ($c = 2.7$, $CDCl_3$).

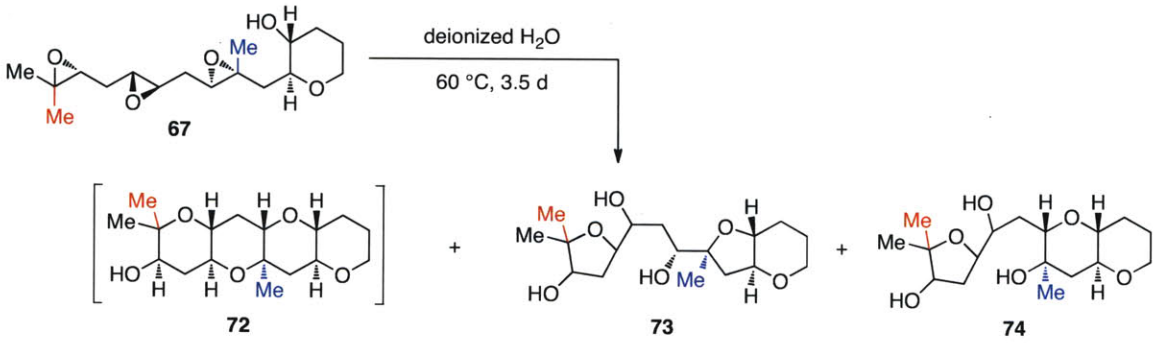
IR (thin film, NaCl) 3443, 2958, 2930, 2855, 1460, 1380, 1253, 1096 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 3.88-3.82 (m, 1H), 3.35-3.22 (m, 2H), 3.11-3.05 (m, 1H), 2.97-2.80 (m, 5H), 2.09-2.03 (m, 2H), 1.83-1.59 (m, 8H), 1.31 (s, 3H), 1.30 (s, 3H), 1.23 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 80.2, 69.9, 67.8, 61.1, 60.0, 59.8, 58.6, 56.0, 55.8, 40.8, 32.8, 32.1, 31.8, 25.8, 24.8, 18.9, 17.7.

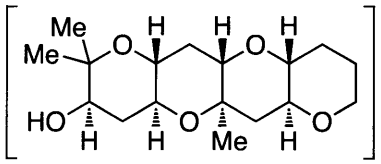
HR-MS (ESI) *m/z* calcd for $C_{17}H_{28}O_5$ $(M+Na)^+$: 335.1829, found 335.1815.

Reaction of triepoxy alcohol 67 to products 72, 73, and 74:



A sample of triepoxy alcohol **67** (44 mg, 0.14 mmol, in 10:1 overall diastereopurity) was suspended in deionized water (7.0 mL) in a 20 mL scintillation vial and stirred vigorously. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60 °C for 92 h. Triepoxy alcohol **67** appeared insoluble in water at room temperature, but dissolved upon heating to give a clear, colorless solution. Over the 3.5 days of heating, the solution gradually became cloudy. After 3.5 days, the reaction was cooled to room temperature.

The aqueous solution was cooled and concentrated *in vacuo* (10 torr, 40 °C). The crude mixture of many products was chromatographed (SiO_2 packed in 5% MeOH in $CHCl_3$ and eluted with 10% MeOH in $CHCl_3$) to provide a sample of THP tetrad **72** contaminated with a co-eluting impurity (5.1 mg, R_f = 0.54 (10% MeOH in $CHCl_3$)) along with 6,6-fused side product **74** (9.7 mg, 0.029 mmol, 21%, R_f = 0.25 (10% MeOH in $CHCl_3$)) and 6,5-fused side product **73** (26.9 mg, 0.081 mmol, 58%, R_f = 0.19 (10% MeOH in $CHCl_3$)). THP tetrad **72** was subjected to a second chromatographic purification (50% EtOAc in hexanes) to provide a sample of **72** in ~70% purity, contaminated with an unknown impurity (2 mg, <5% yield, R_f = 0.45 (100% EtOAc)).



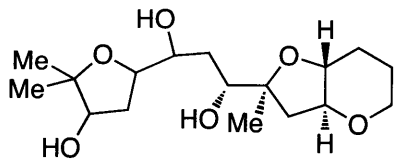
72

THP tetrad 72: This compound was formed in very low yield from the reaction of **67** and could not be isolated cleanly. We were unable to collect full characterization data or confirm its structure.

R_f = 0.45 (100% EtOAc), 0.54 (10% MeOH in $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.96-3.90 (m, 1H), 3.58-3.51 (m, 1H), 3.43-3.34 (m, 2H), 3.30-3.21 (m, 2H), 3.17 (ddd, *J* = 11.2, 9.3, 4.6 Hz, 1H), 3.11 (ddd, *J* = 11.0, 9.1, 4.0 Hz, 1H), 2.15-2.06 (m, 3H), 2.04 (app dt, *J* = 11.5 Hz, 4.1 Hz, 1H), 1.79-1.70 (m, 2H), 1.62-1.45 (m, 4H), 1.30 (s, 3H), 1.30 (s, 3H), 1.21 (s, 3H).

HR-MS (ESI) *m/z* calcd for $C_{17}H_{28}O_5$ $(M+Na)^+$: 335.1829, found 335.1820.



73

6,5-Fused side product 73:

R_f = 0.19 (10% MeOH in $CHCl_3$).

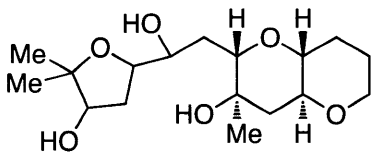
$[\alpha]^{22}_D$ = -3.3 (*c* = 0.36, CH_2Cl_2).

IR (thin film, NaCl): 3418, 2927, 2872, 1456, 1378, 1287, 1123, 1064, 968 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (ddd, J = 8.8, 6.6, 4.1 Hz, 1H), 4.02-3.96 (m, 3H), 3.87 (app d, J = 10.2 Hz, 1H), 3.47 (app td, J = 11.8, 3.1 Hz, 1H), 3.36 (ddd, J = 10.9, 9.0, 3.8 Hz, 1H), 3.28 (ddd, J = 11.0, 9.0, 6.5 Hz, 1H), 2.54 (s, 1H), 2.41 (s, 1H), 2.26 (ddd, J = 13.2, 8.8, 6.1 Hz, 1H), 2.23-2.18 (m, 1H), 2.11 (app t, J = 11.1 Hz, 1H), 1.89-1.82 (m, 2H), 1.74-1.47 (m, 4H), 1.44 (ddd, J = 13.9, 10.3, 3.4 Hz, 1H), 1.26 (s, 3H), 1.24-1.22 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 84.0, 83.3, 81.0, 79.9, 79.6, 78.3, 74.2, 69.6, 69.0, 36.6, 34.6, 34.5, 30.3, 27.9, 25.1, 24.7, 21.6.

HR-MS (ESI) *m/z* calcd for $C_{17}H_{30}O_6$ $(M+Na)^+$: 353.1935, found 353.1944.



74

6,6-Fused side product 74:

R_f = 0.25 (10% MeOH in $CHCl_3$).

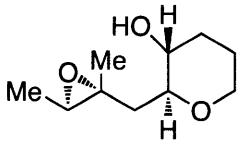
$[\alpha]^{22}_D$ = -12.8 (c = 0.15, CH_2Cl_2).

IR (thin film, NaCl) 3413, 2929, 2867, 1462, 1378, 1287, 1101, 1049, 944 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05-3.97 (m, 2H), 3.94-3.88 (m, 1H), 3.79 (ddd, J = 8.9, 5.9, 2.6 Hz, 1H), 3.62 (s, 1H), 3.47 (dd, J = 10.4, 2.2 Hz, 1H), 3.41-3.34 (m, 1H), 3.10 (ddd, J = 11.0, 9.1, 4.2 Hz, 1H), 2.99 (ddd, J = 11.8, 9.1, 4.3 Hz, 1H), 2.29 (ddd, J = 13.6, 7.9, 6.1 Hz, 1H), 2.12 (dd, J = 11.7, 4.3 Hz, 1H), 2.07-2.01 (m, 2H), 1.97 (ddd, J = 13.2, 6.9, 3.8 Hz, 1H), 1.76-1.69 (m, 2H), 1.64-1.41 (m, 6H), 1.26 (s, 3H), 1.25 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 85.6, 83.2, 79.6, 79.2, 78.3, 76.5, 74.7, 71.2, 68.1, 45.9, 35.9, 31.9, 29.4, 27.9, 25.6, 22.1, 21.6.

HR-MS (ESI) *m/z* calcd for $C_{17}H_{30}O_6$ $(M+Na)^+$: 353.1935, found 353.1946.



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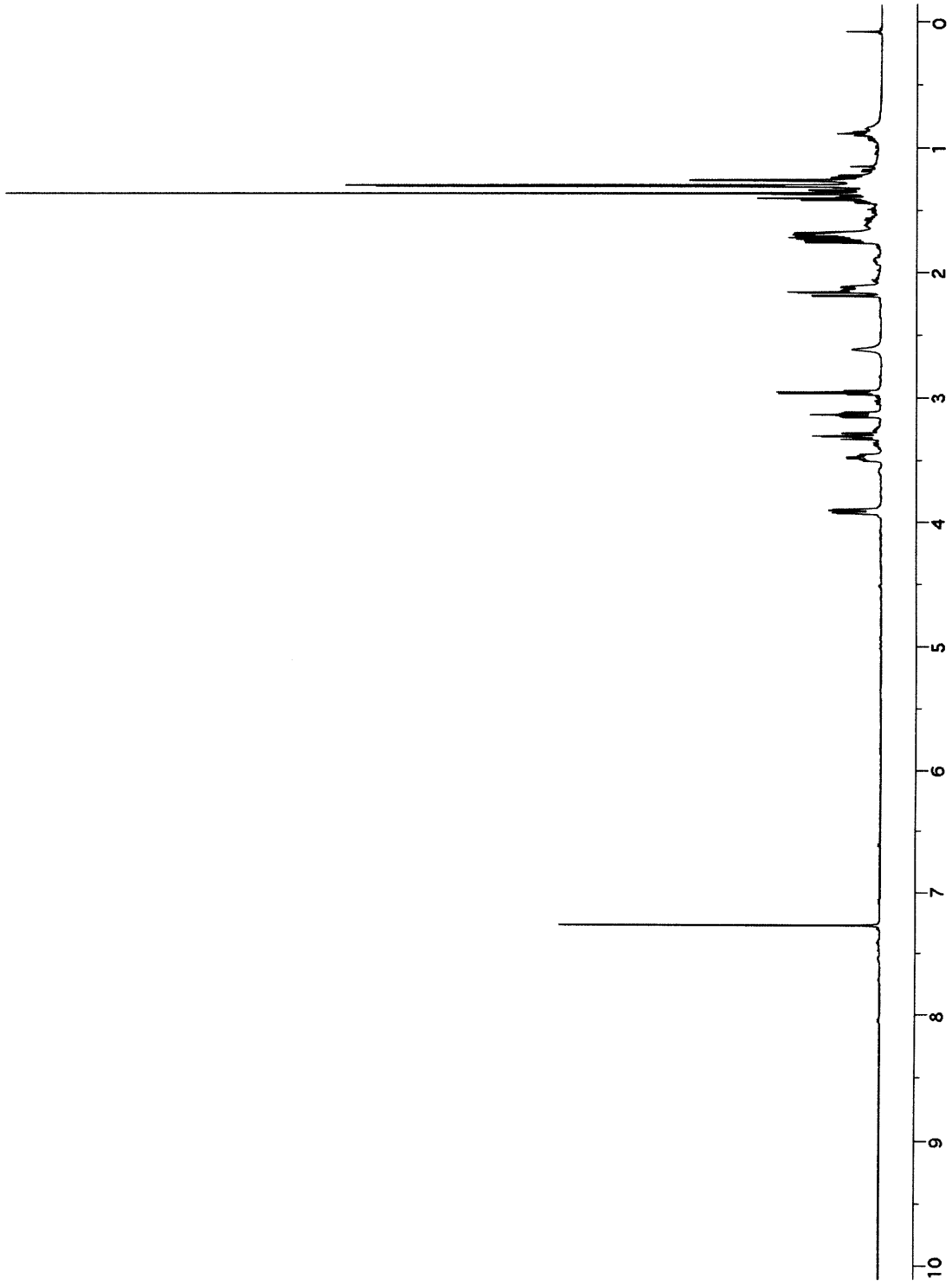

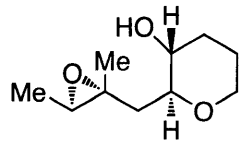

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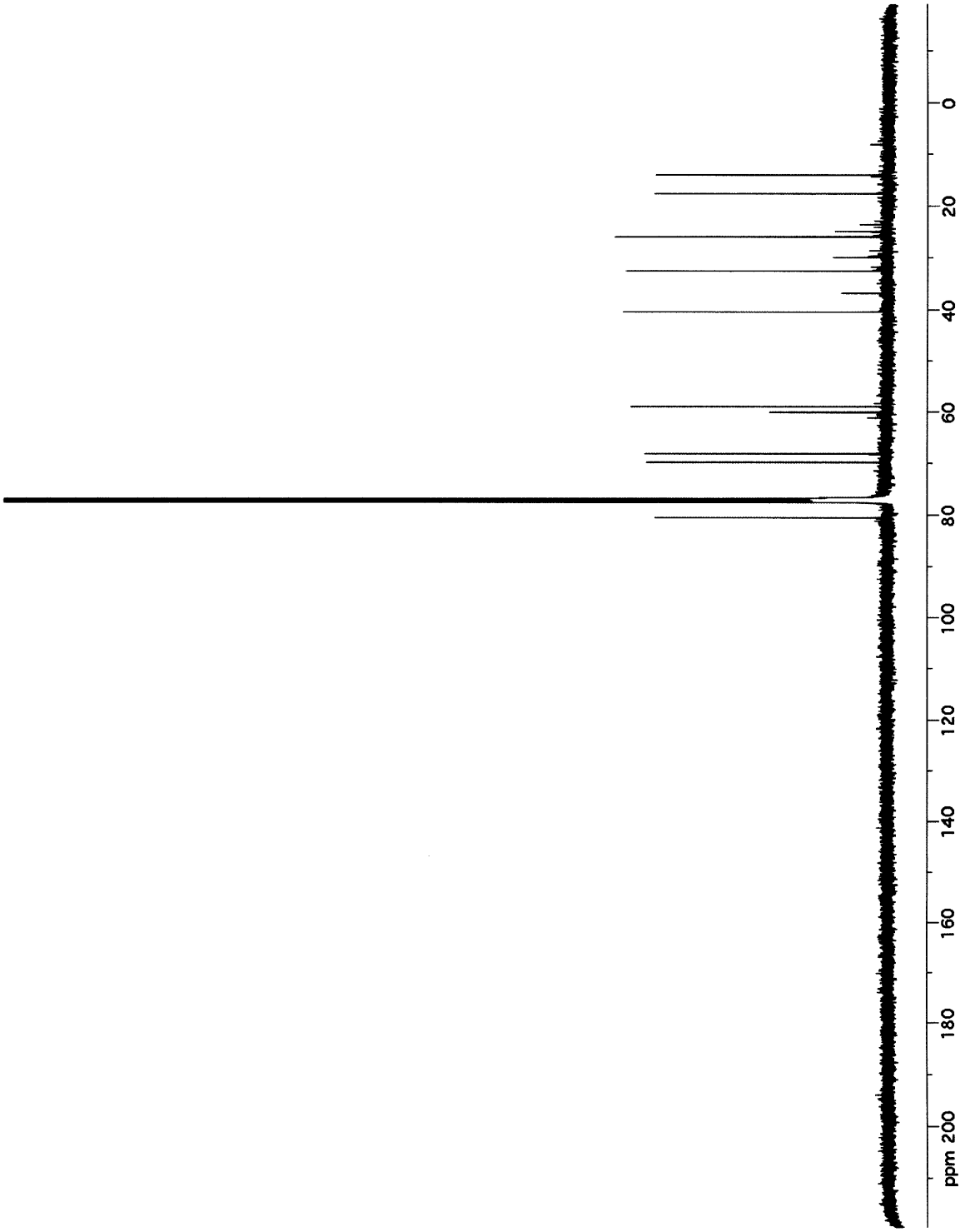

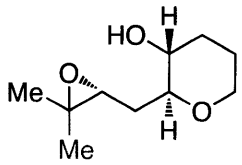

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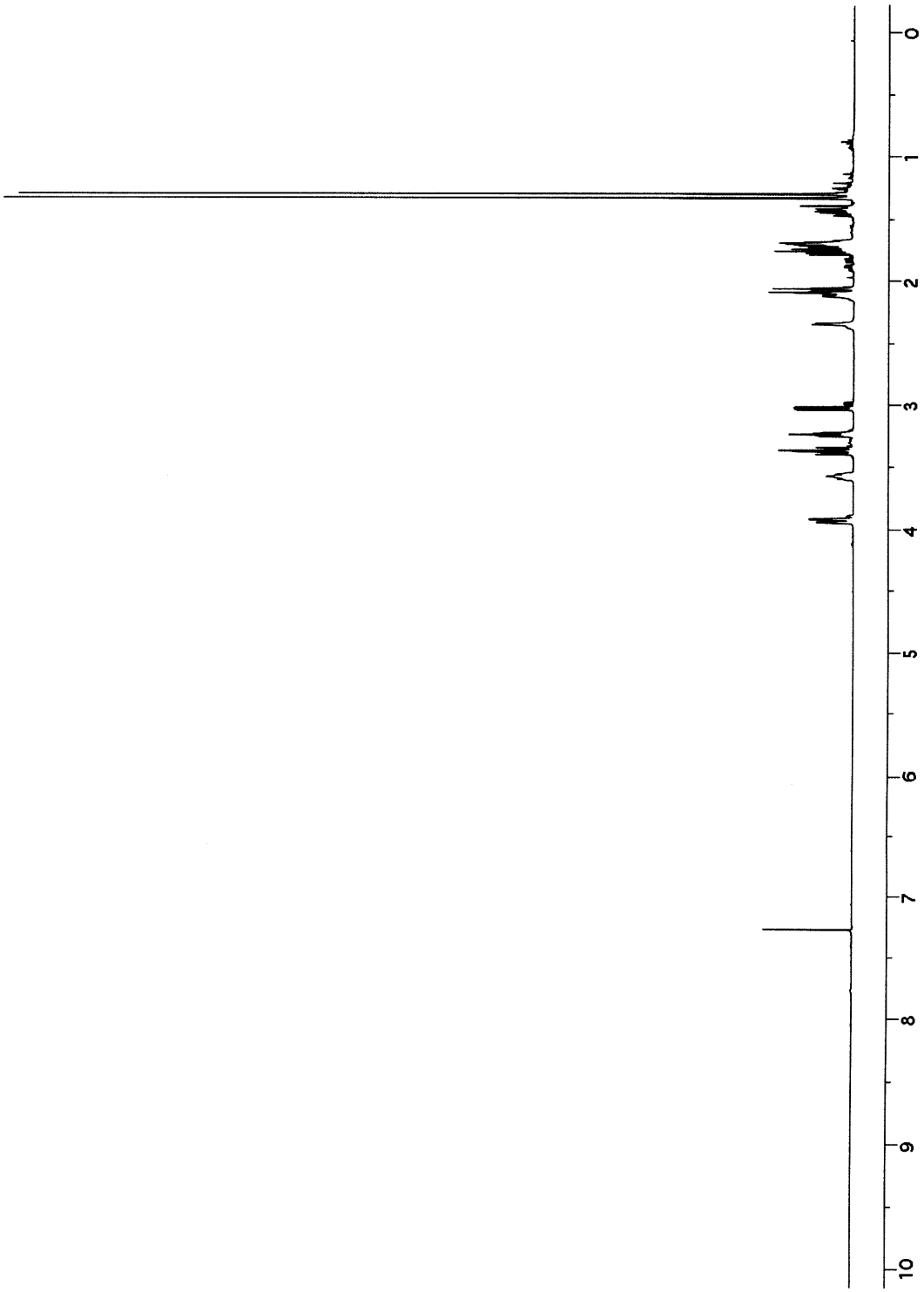

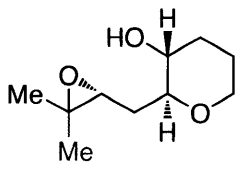
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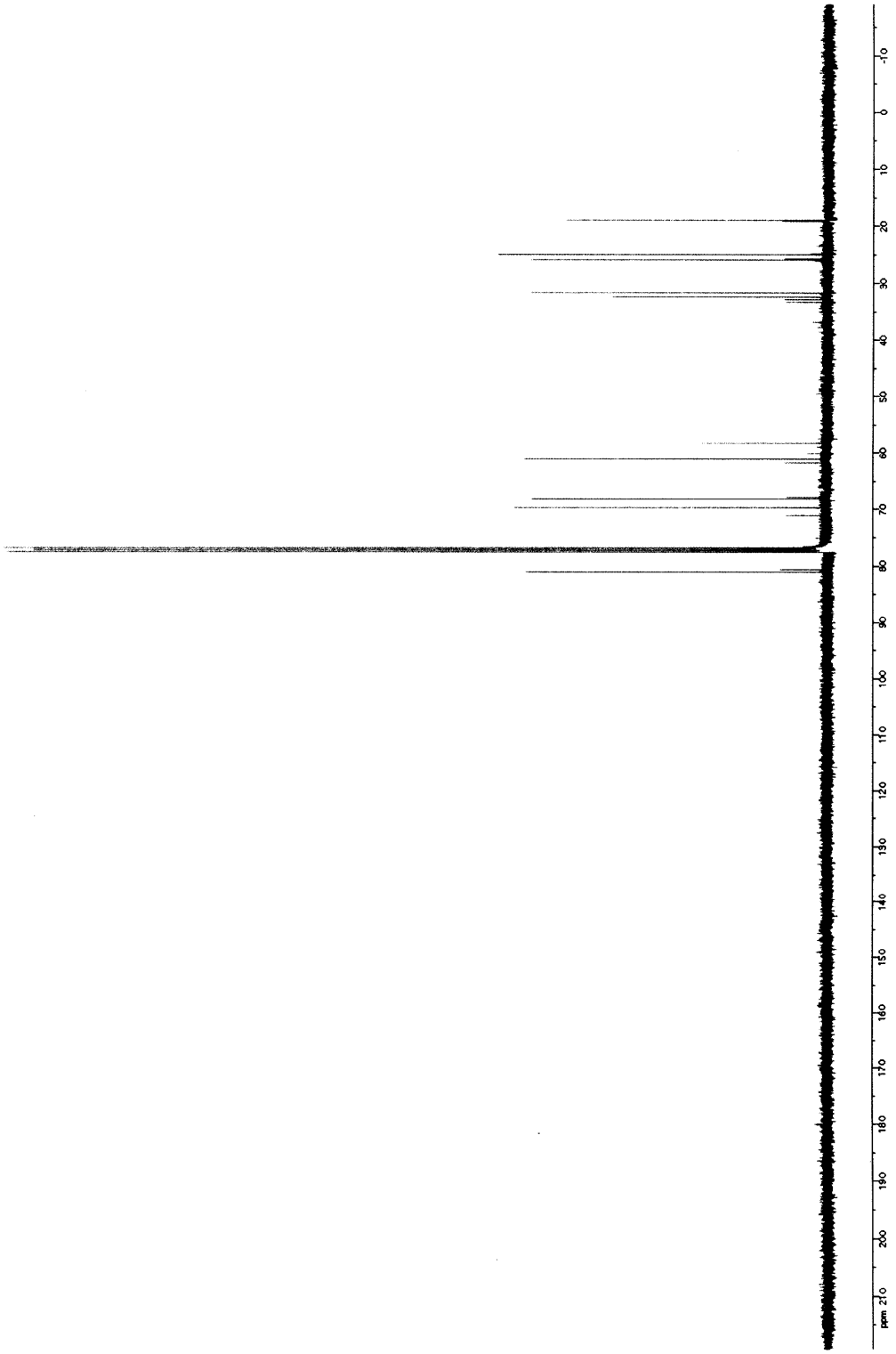
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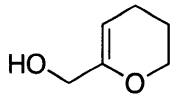

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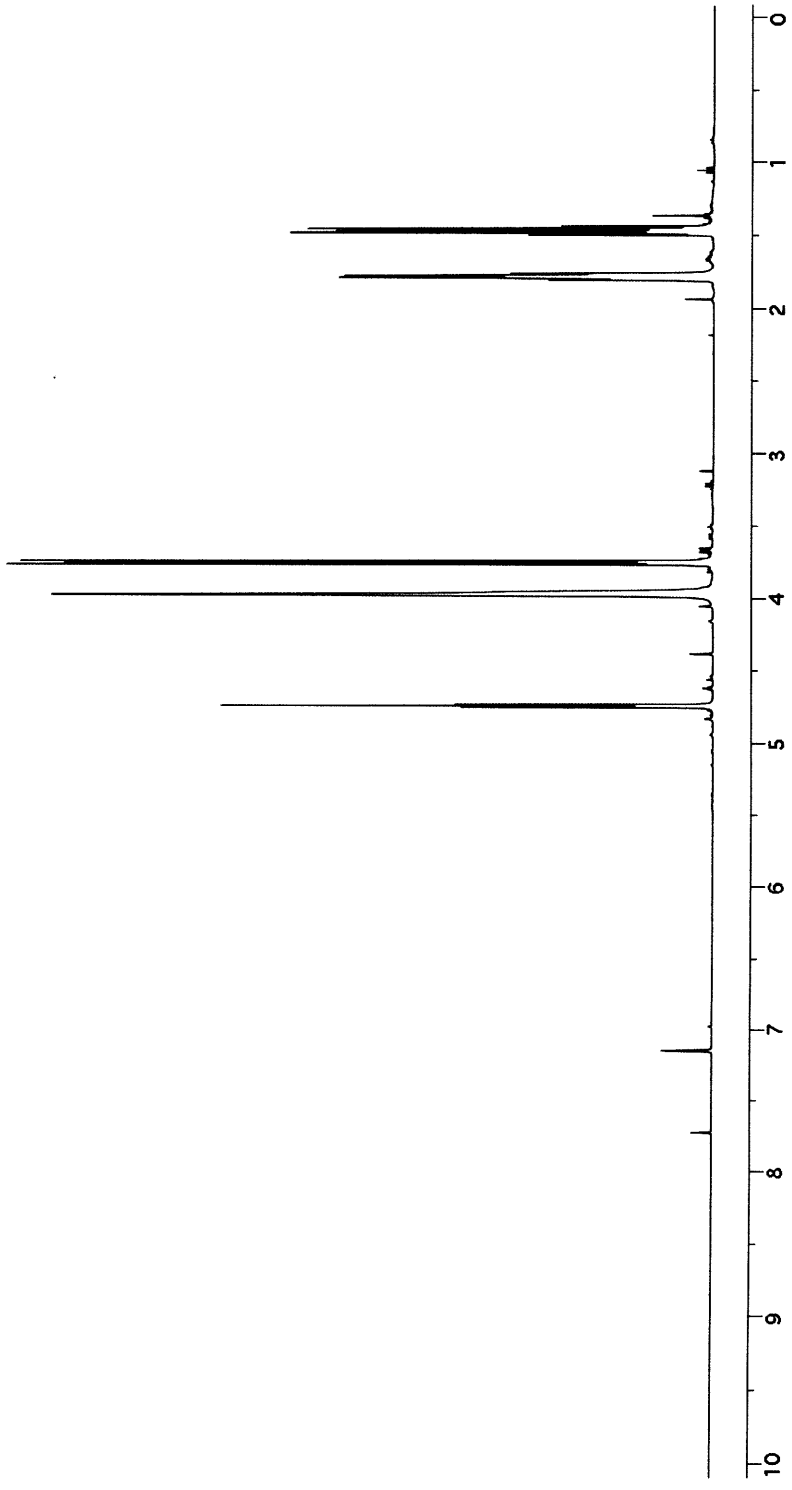

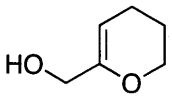

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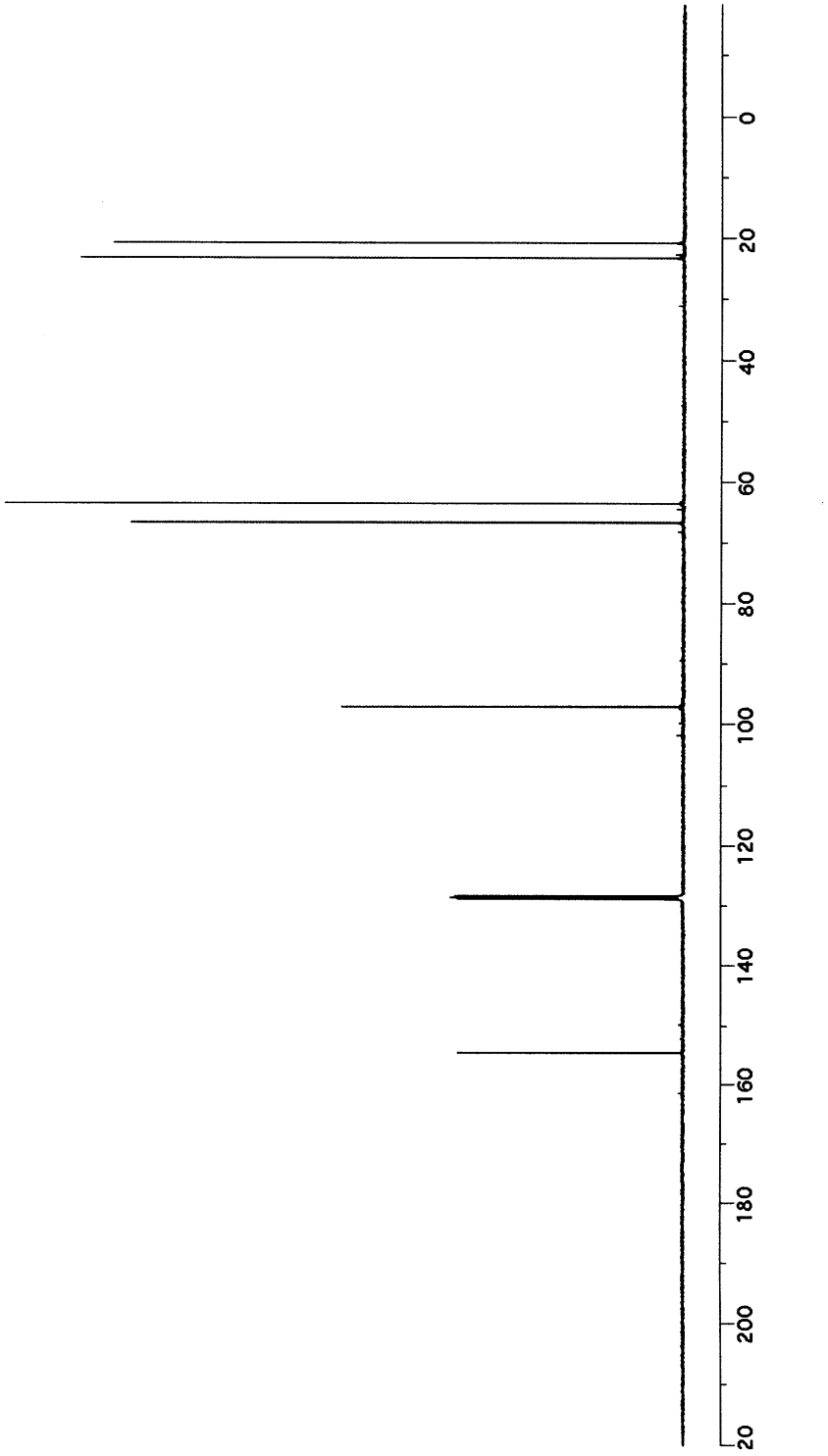

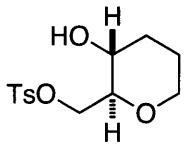

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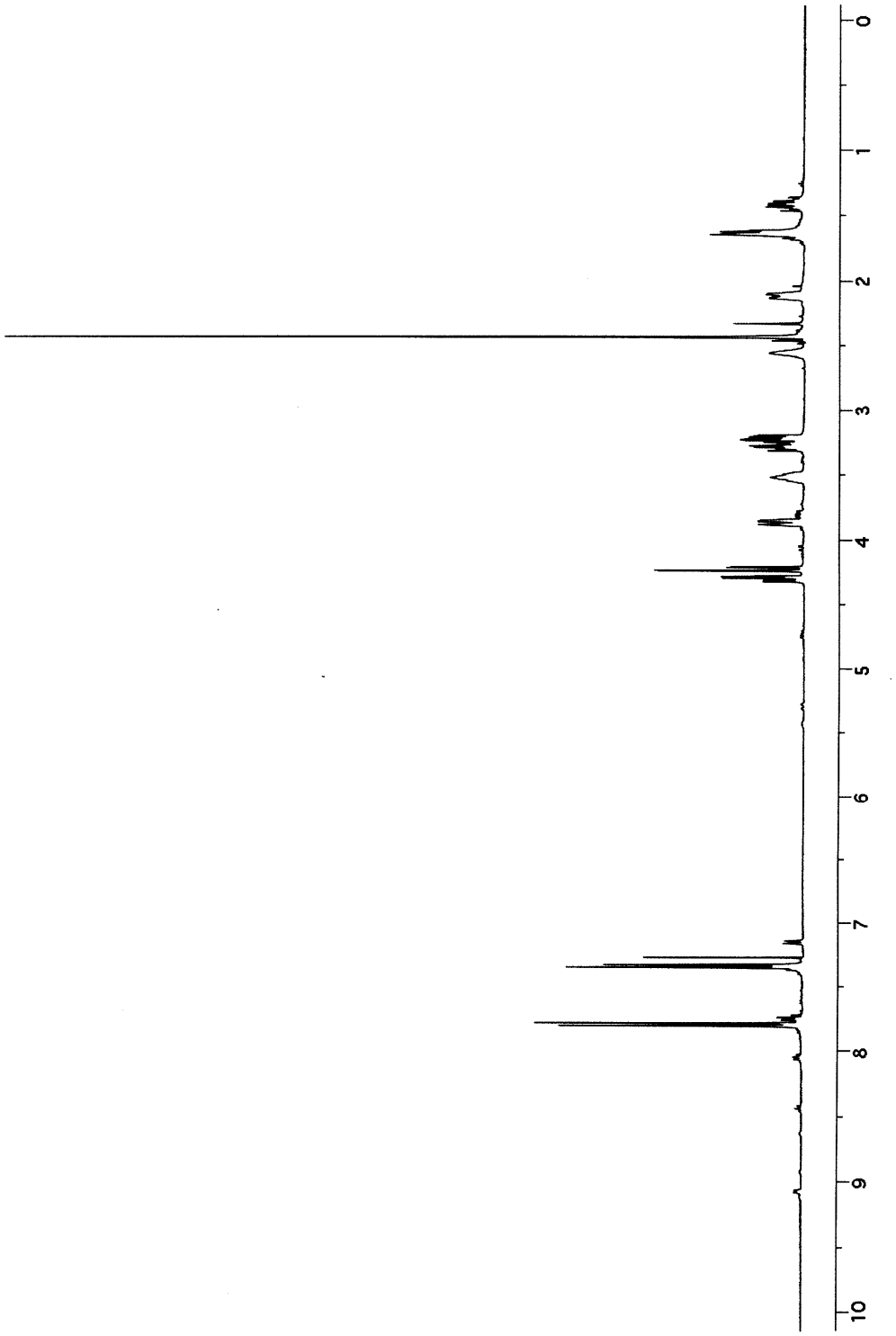

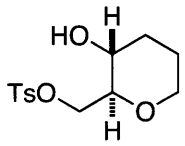

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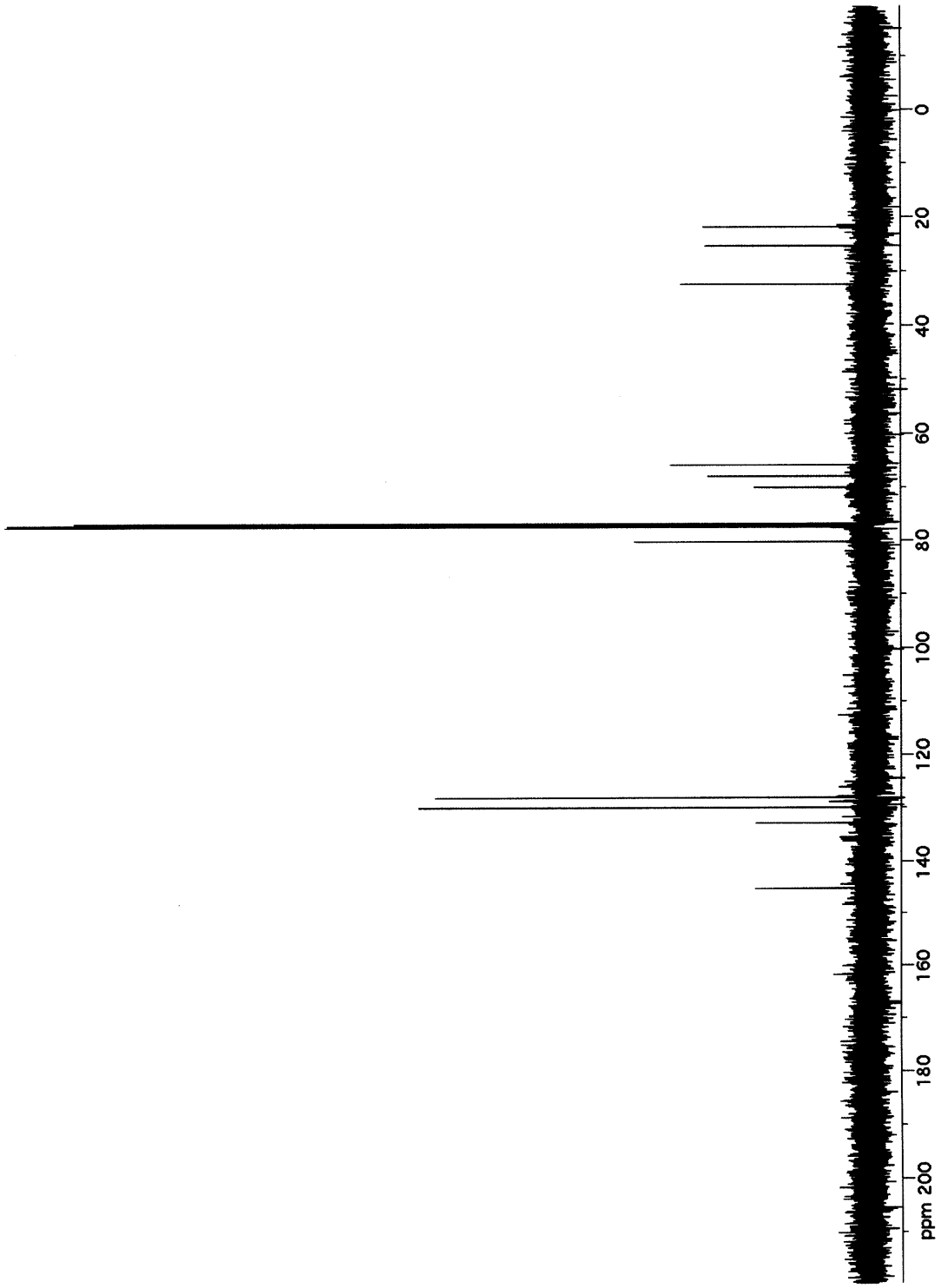

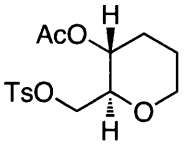

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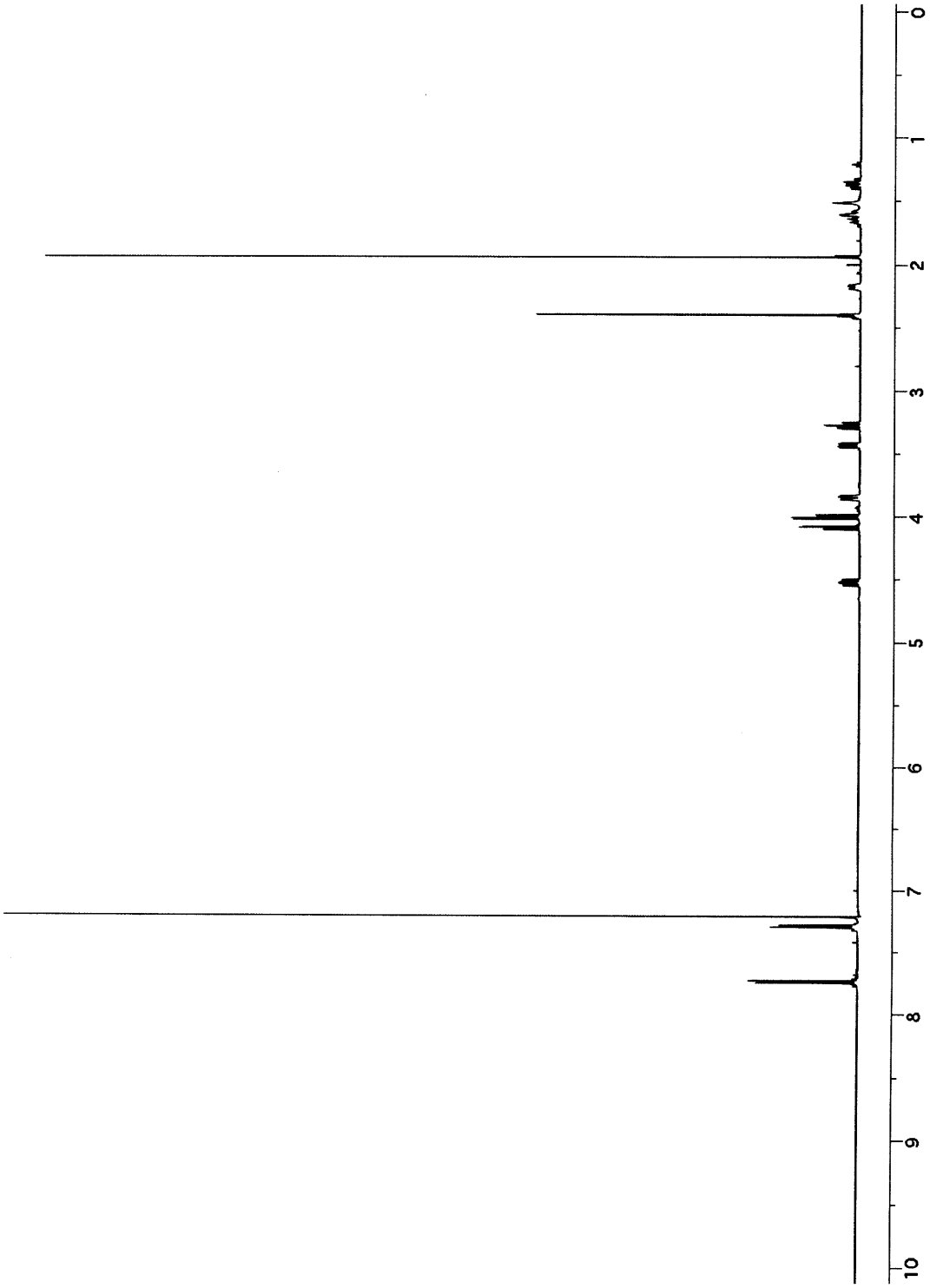

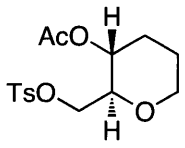

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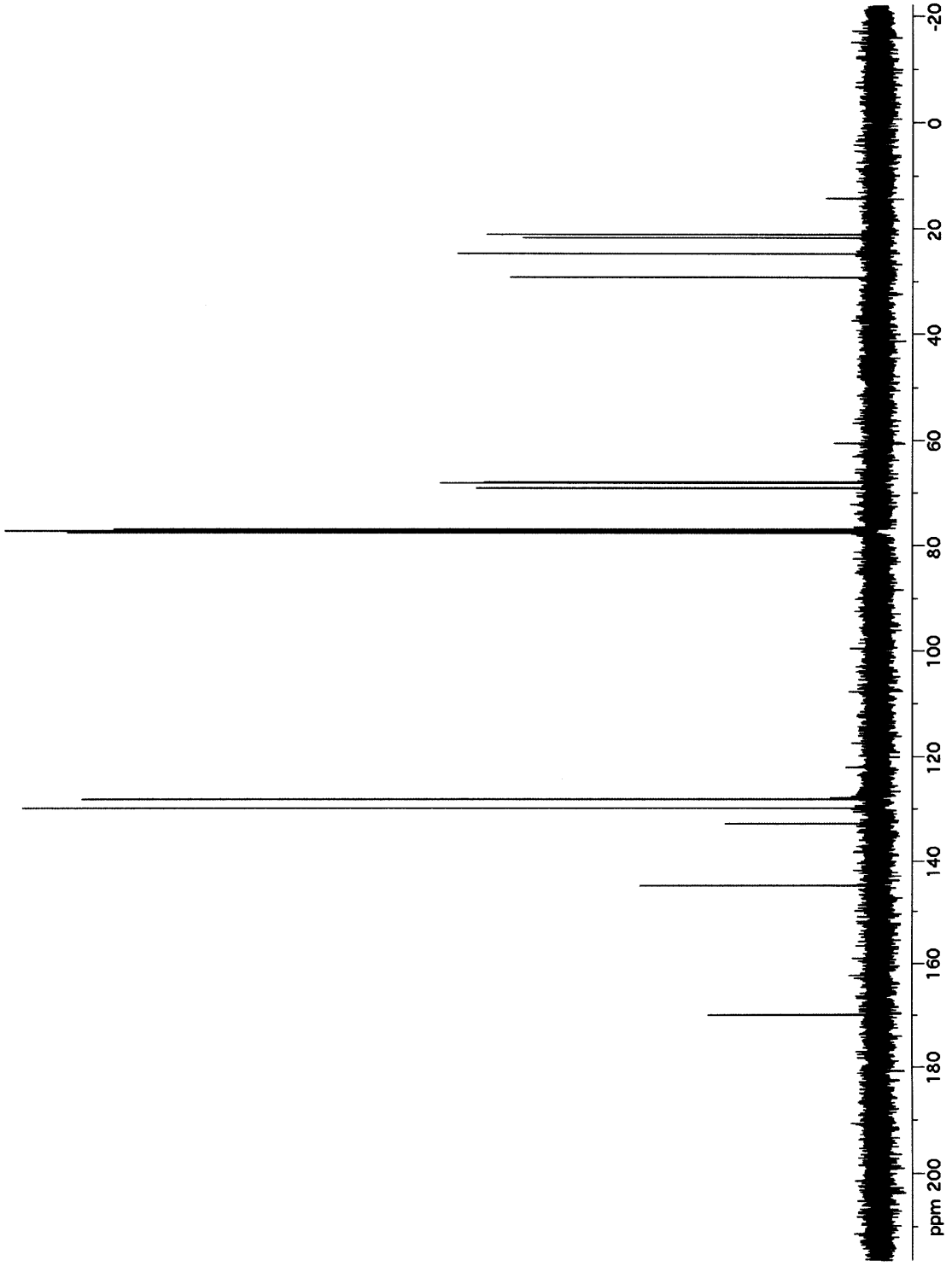

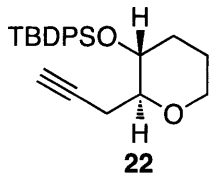

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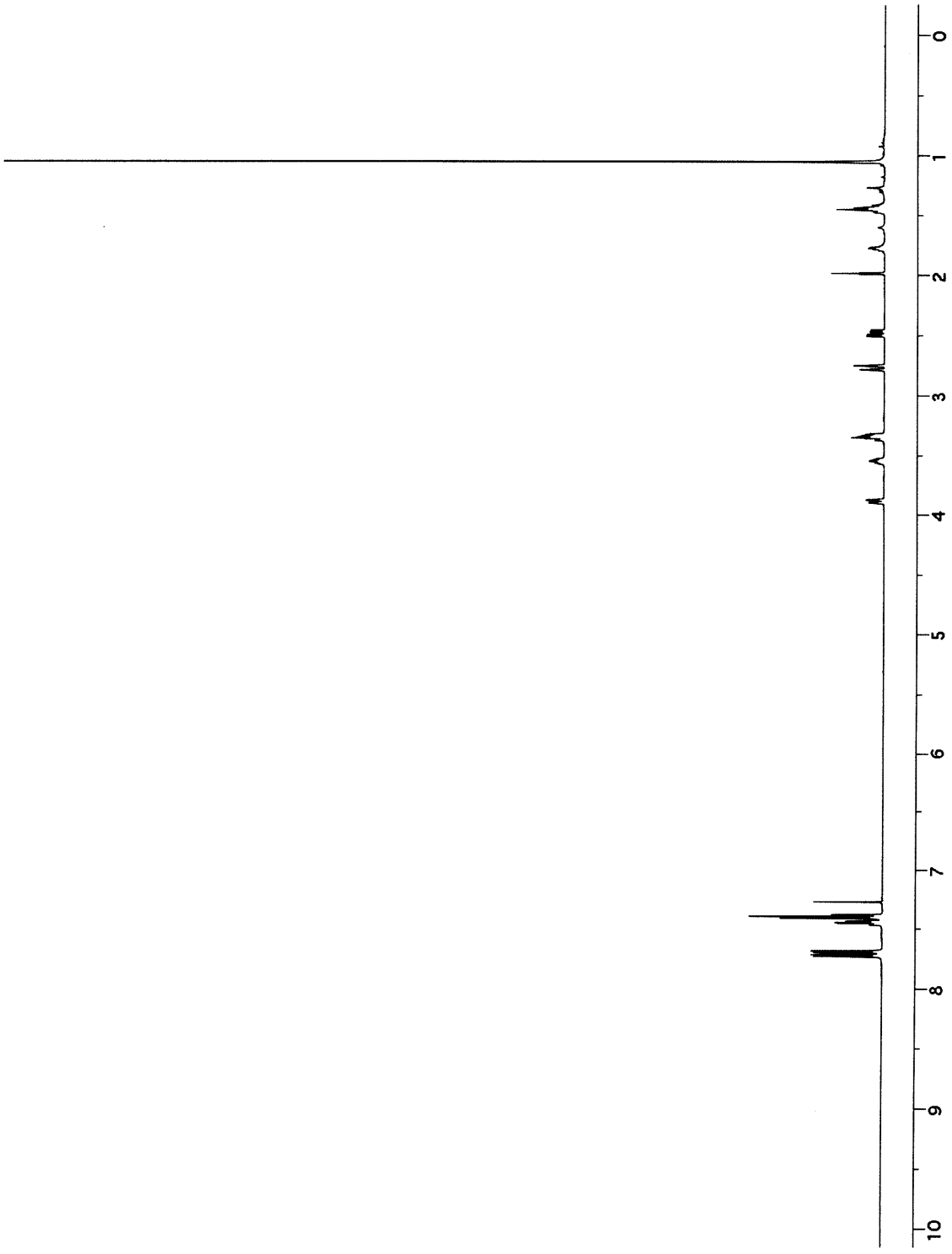

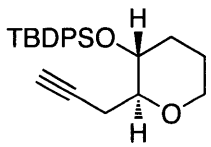
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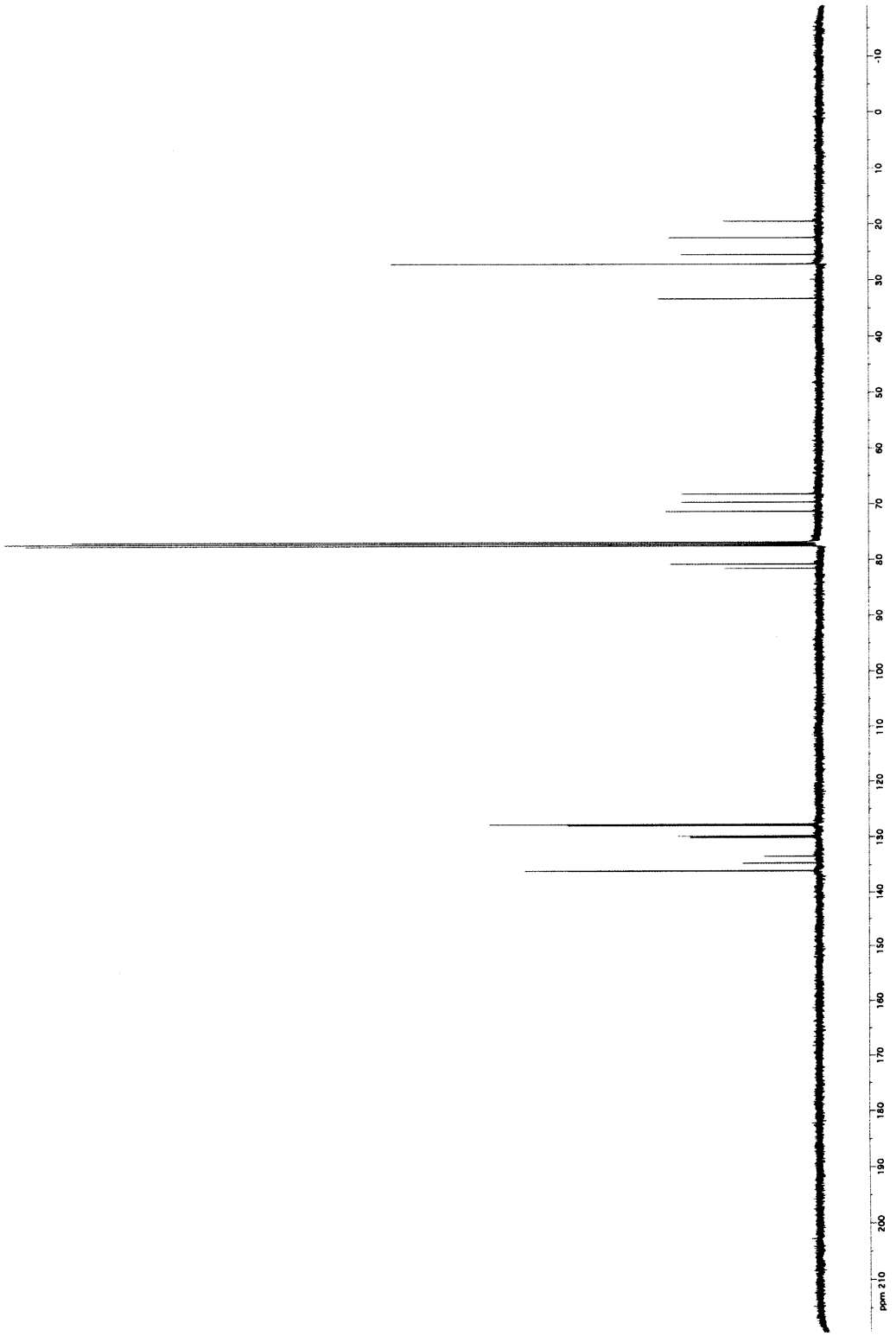
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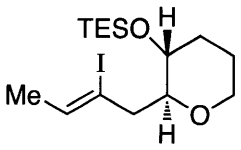

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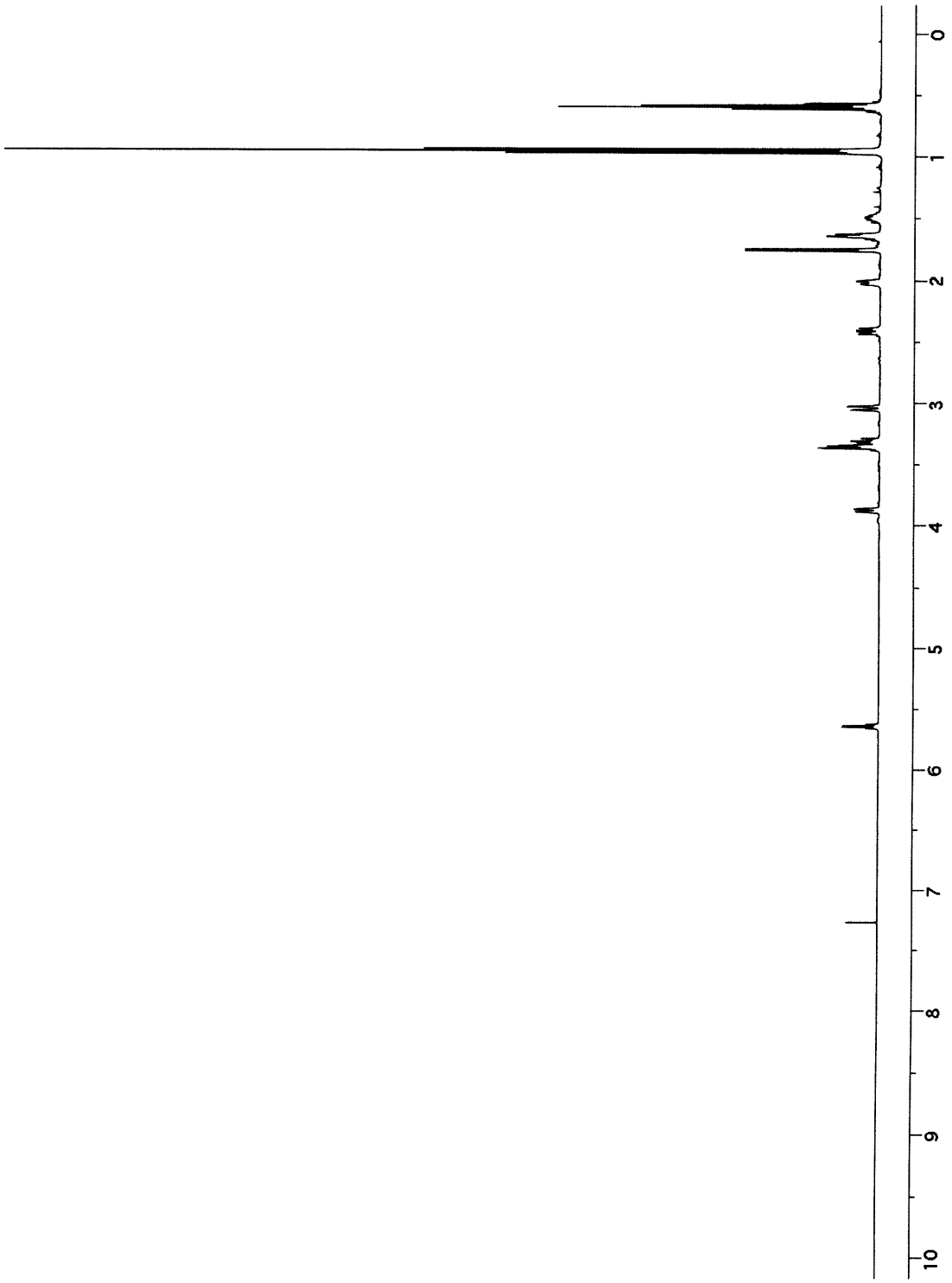

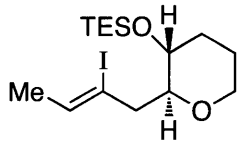

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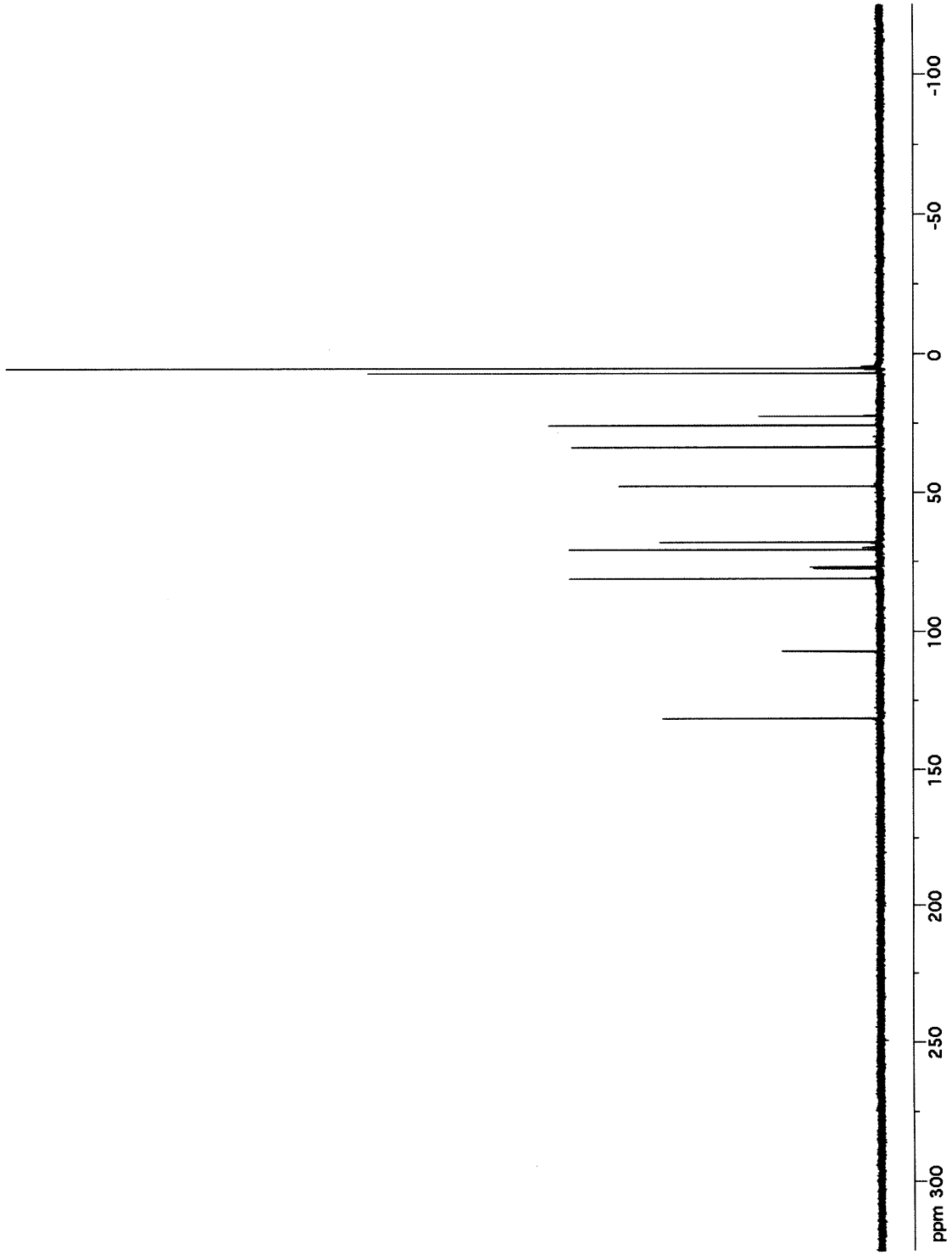

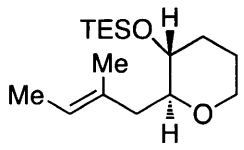

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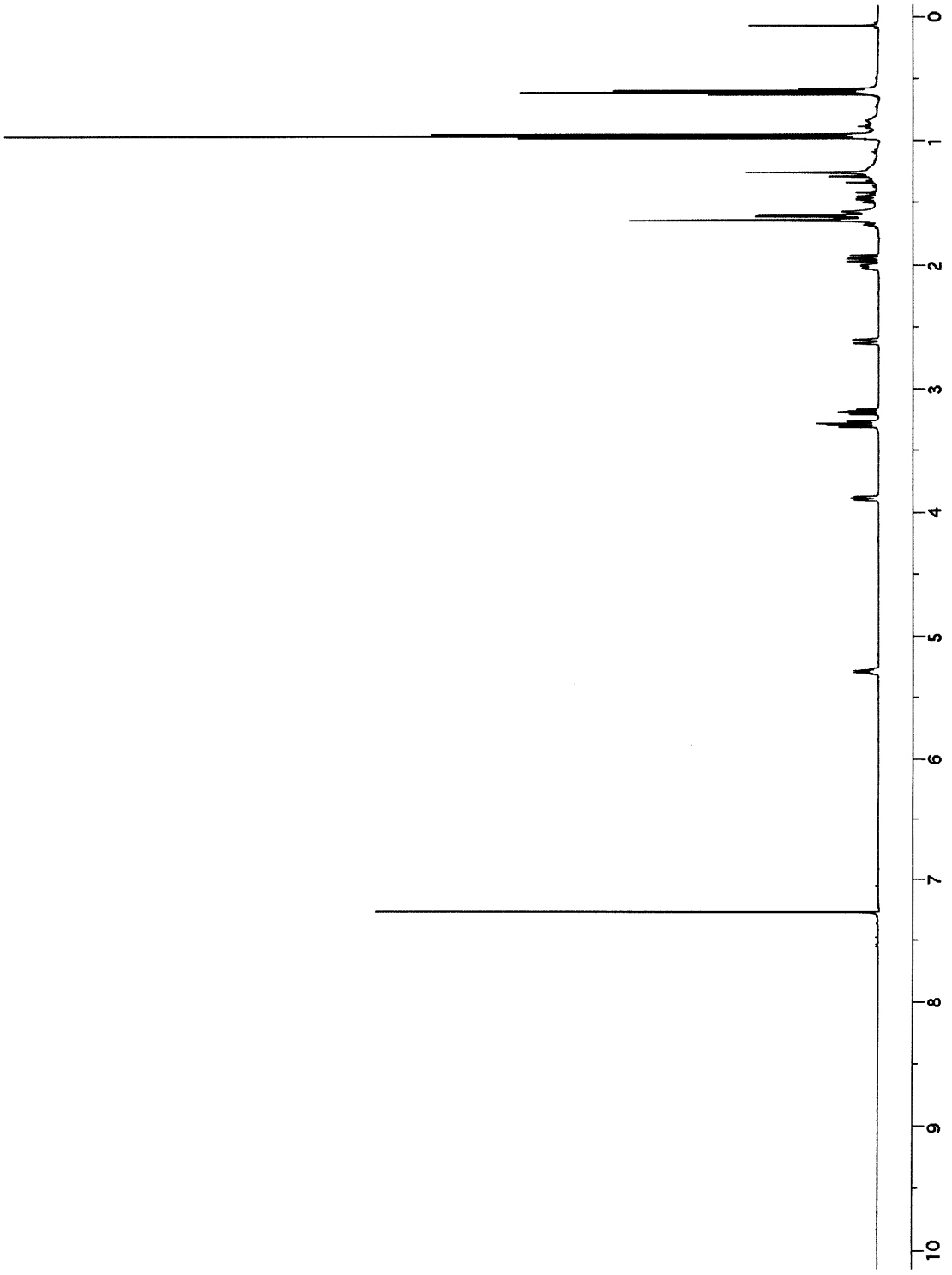

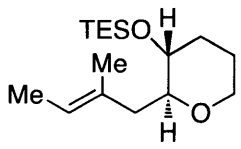

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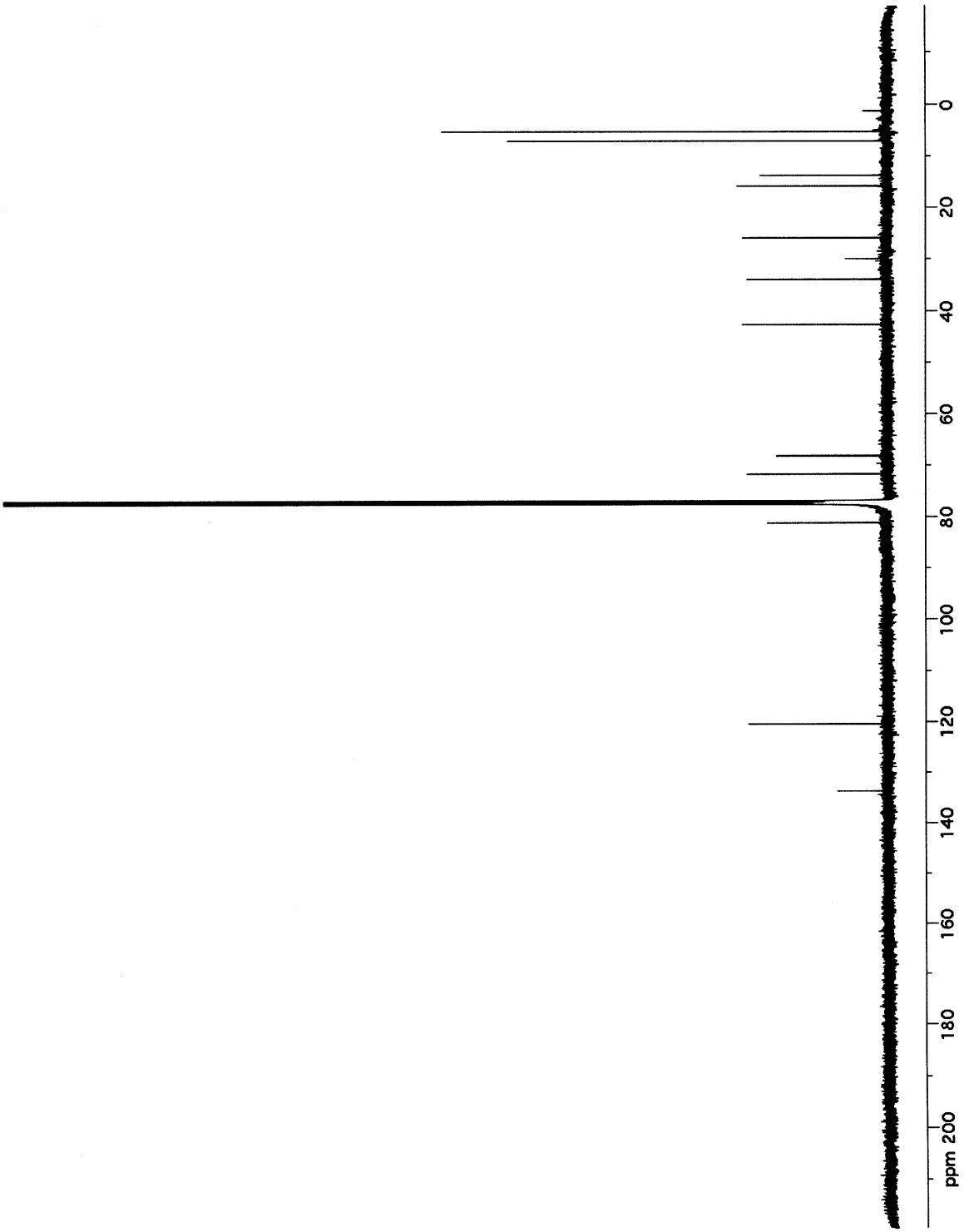

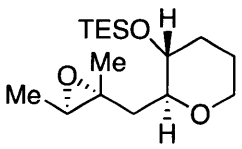

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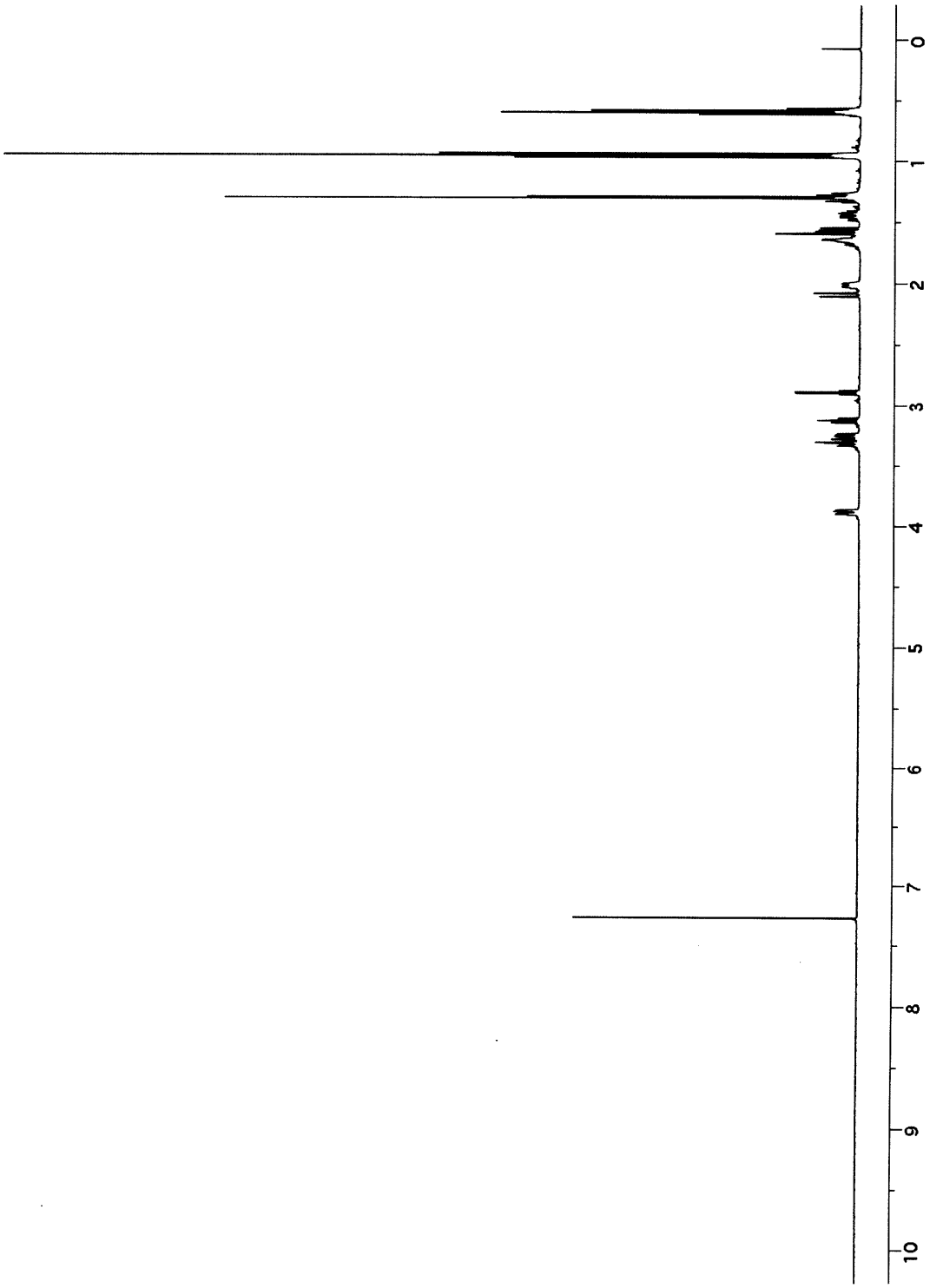

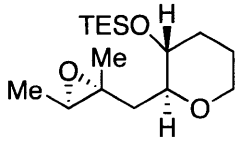

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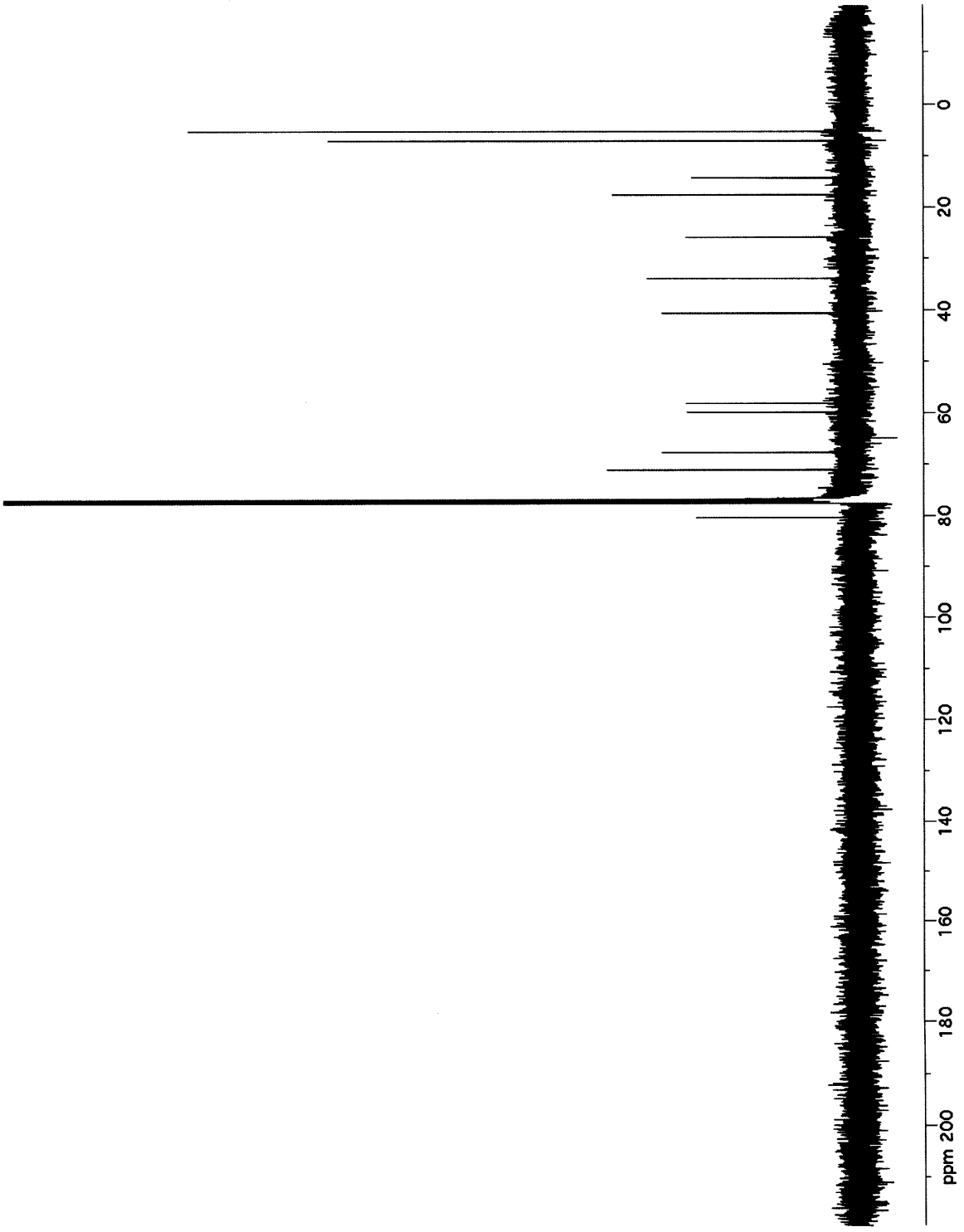

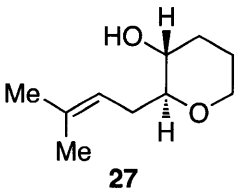

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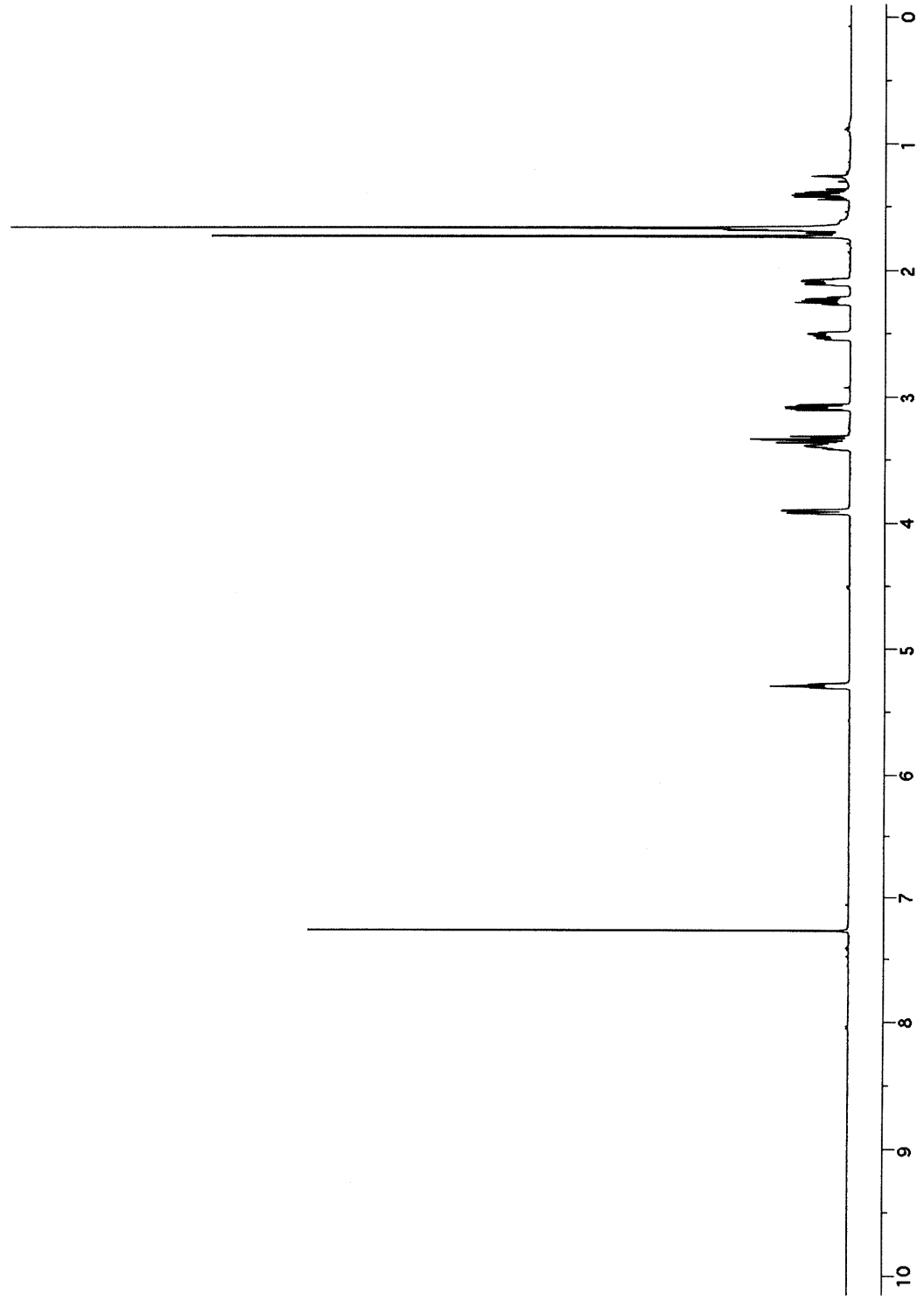

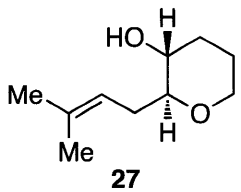

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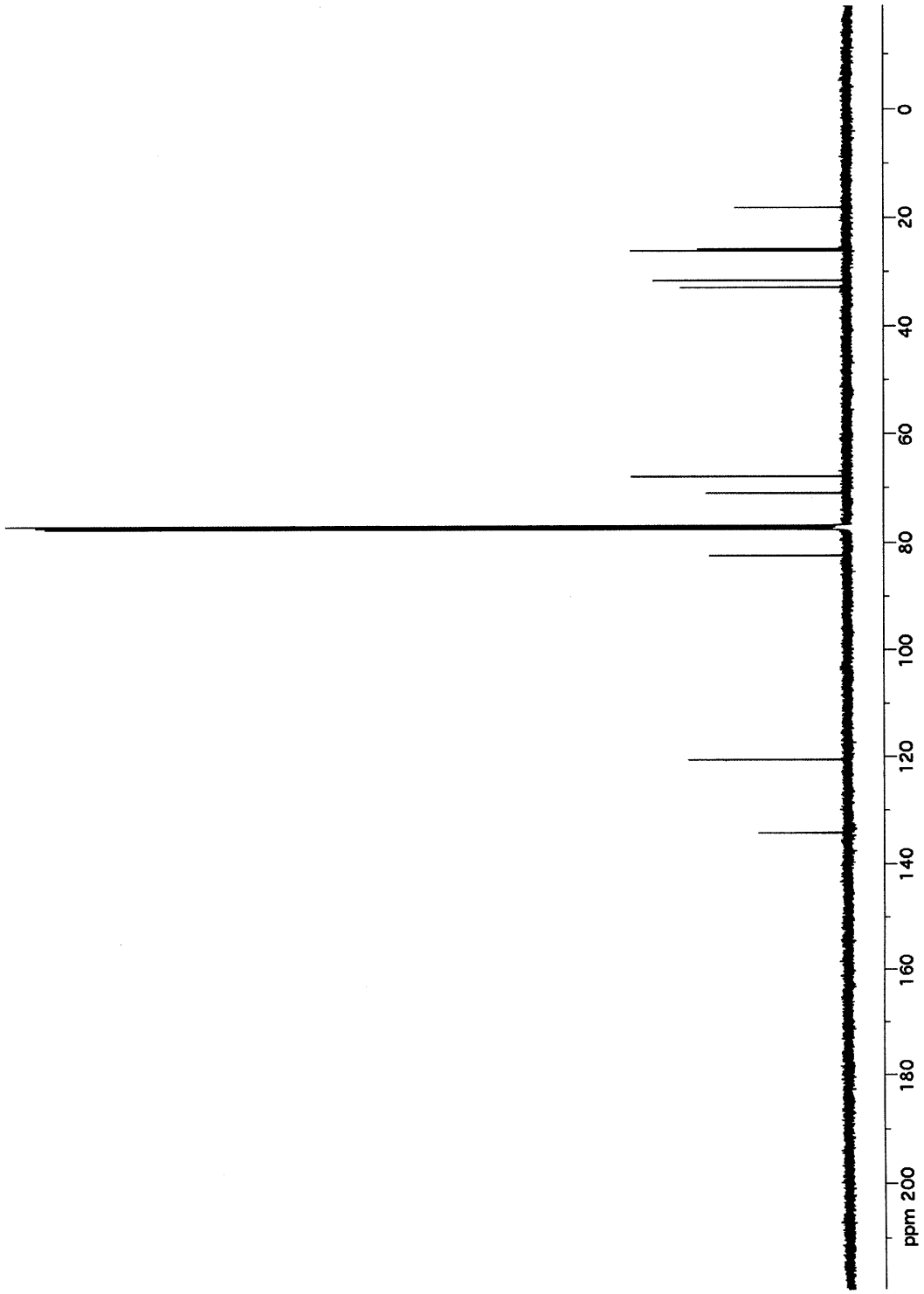

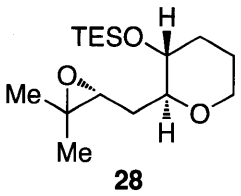

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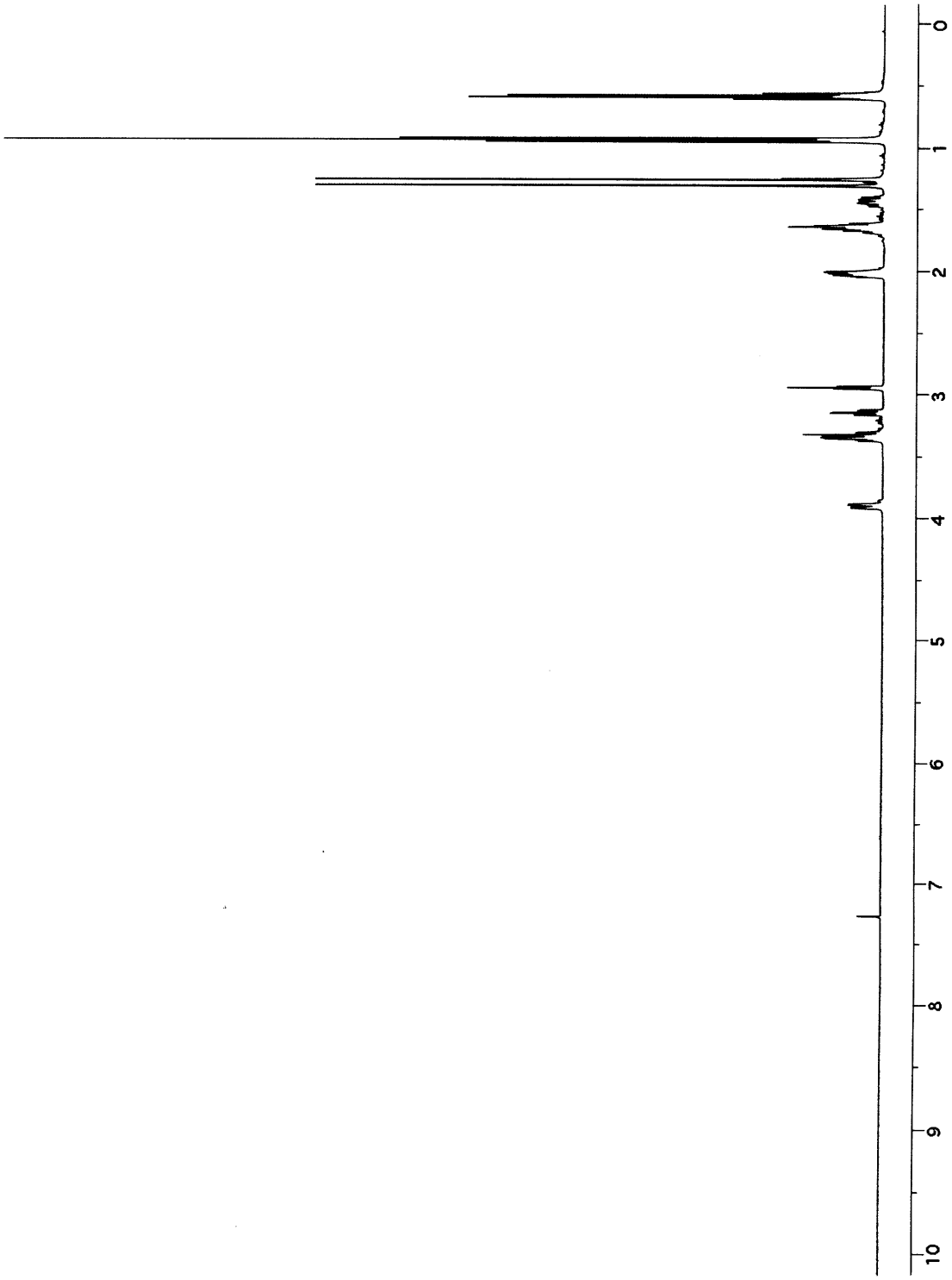

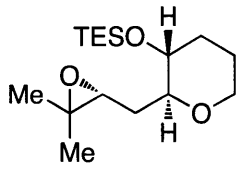

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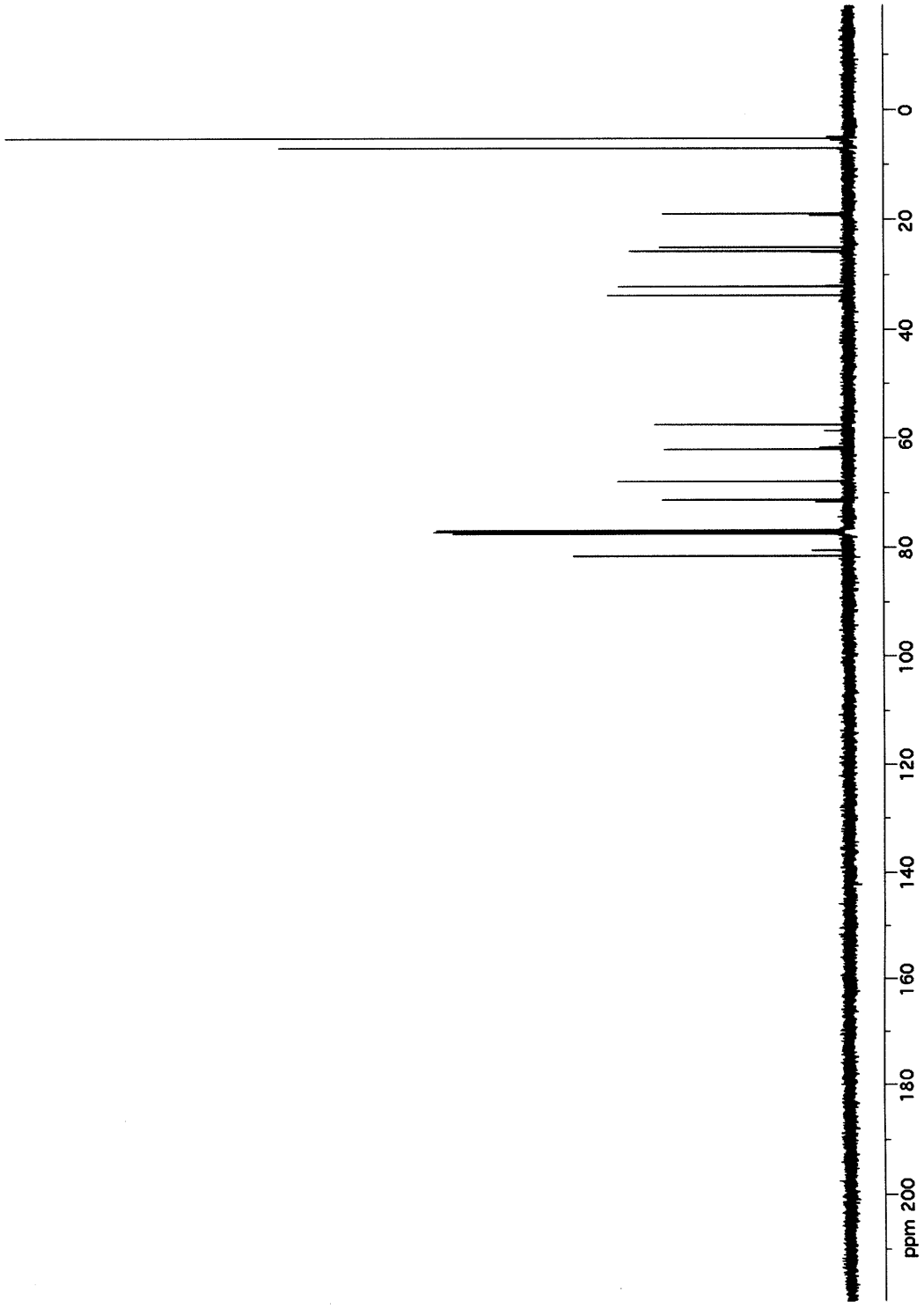

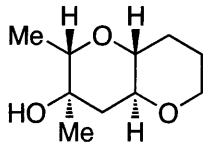

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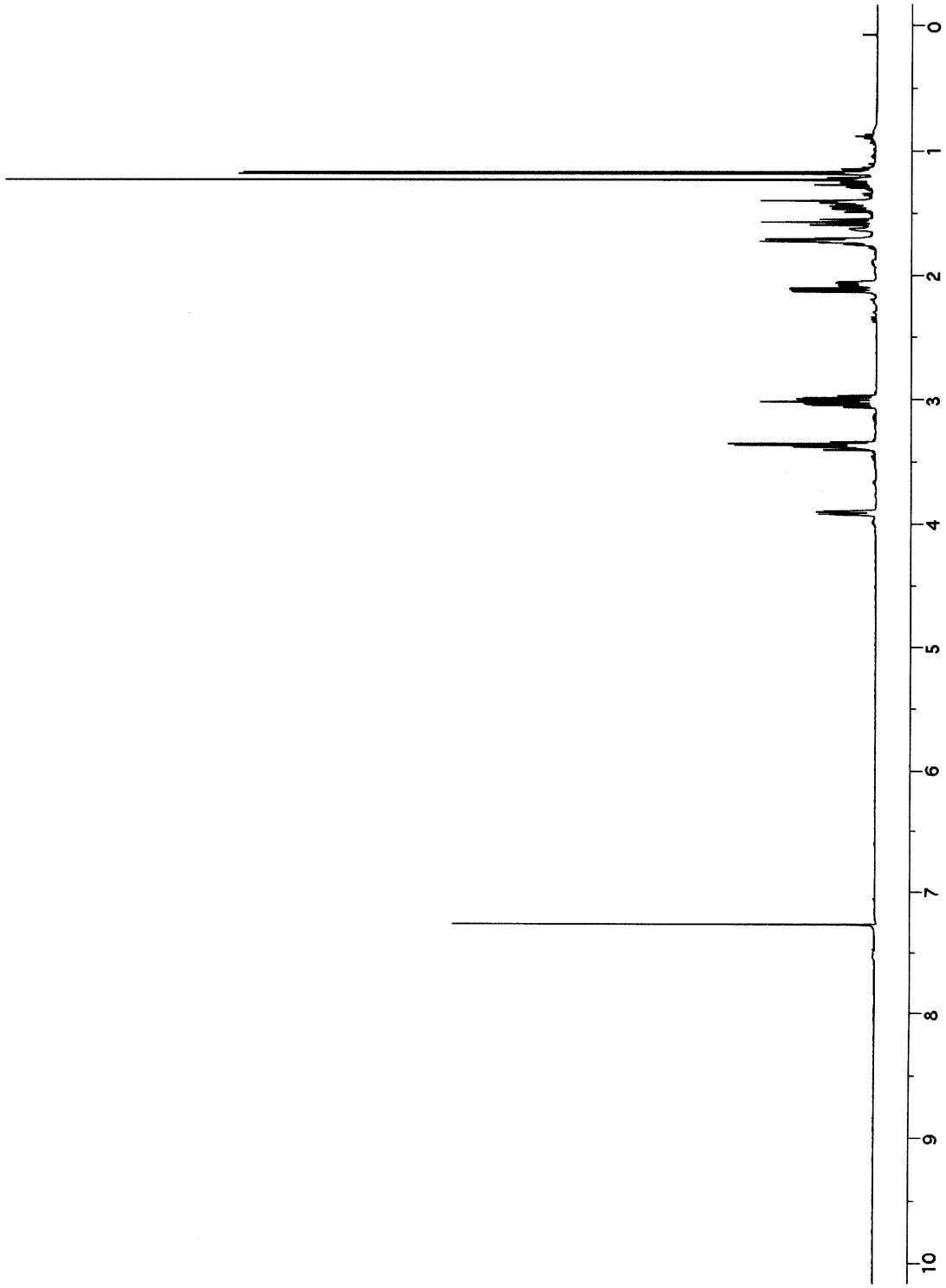

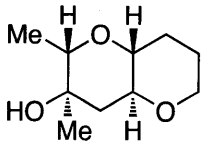

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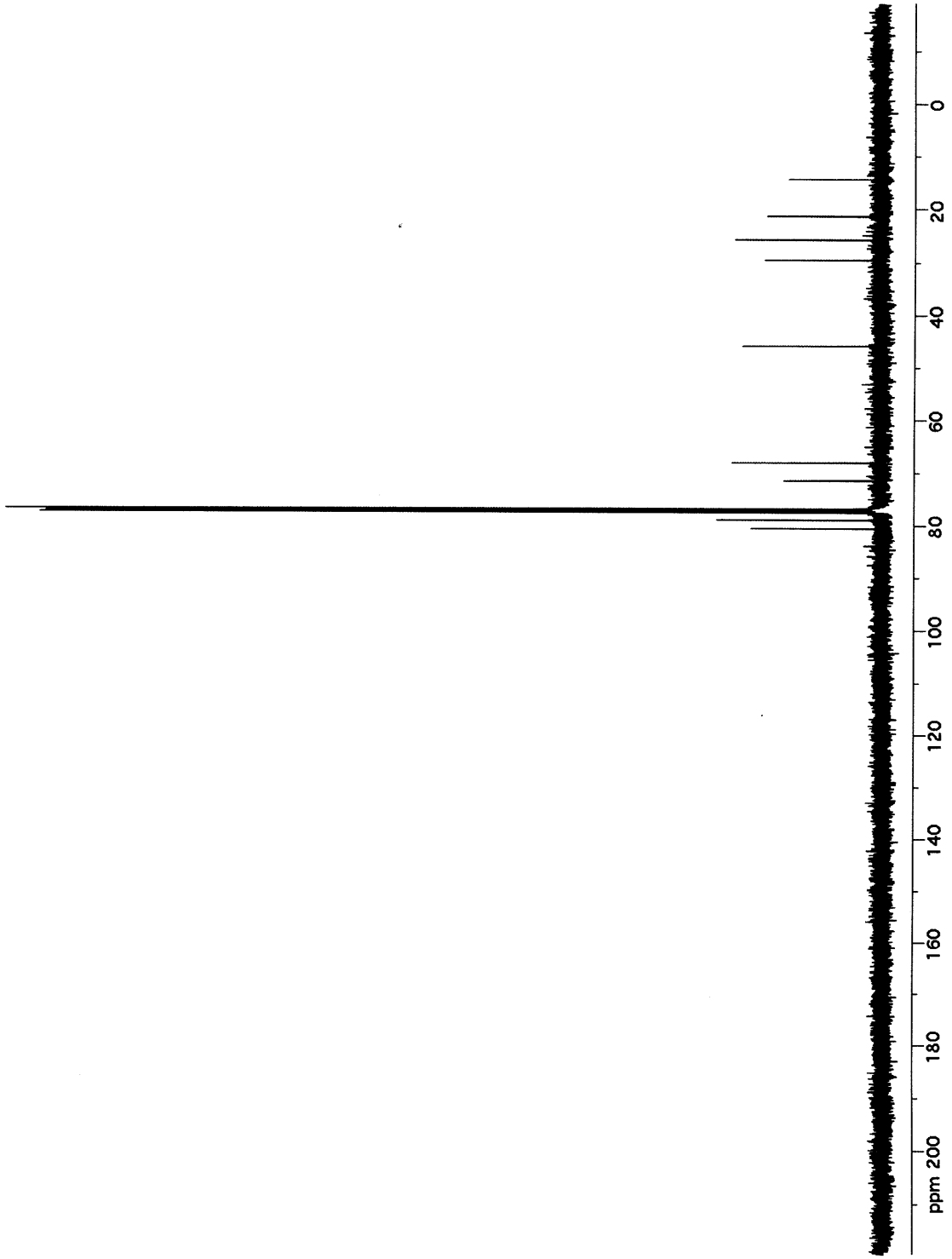

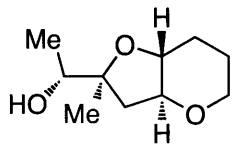

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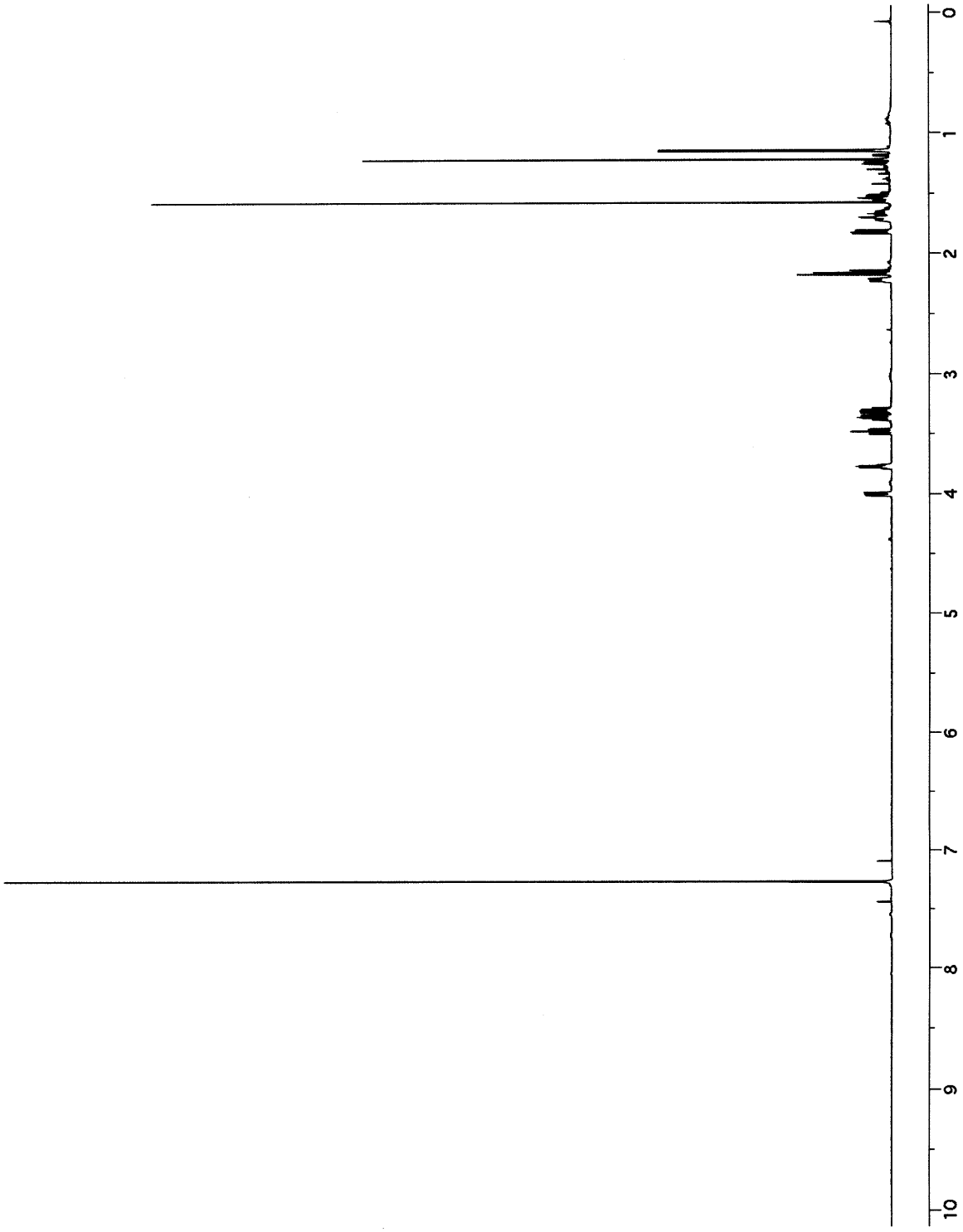

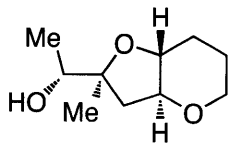

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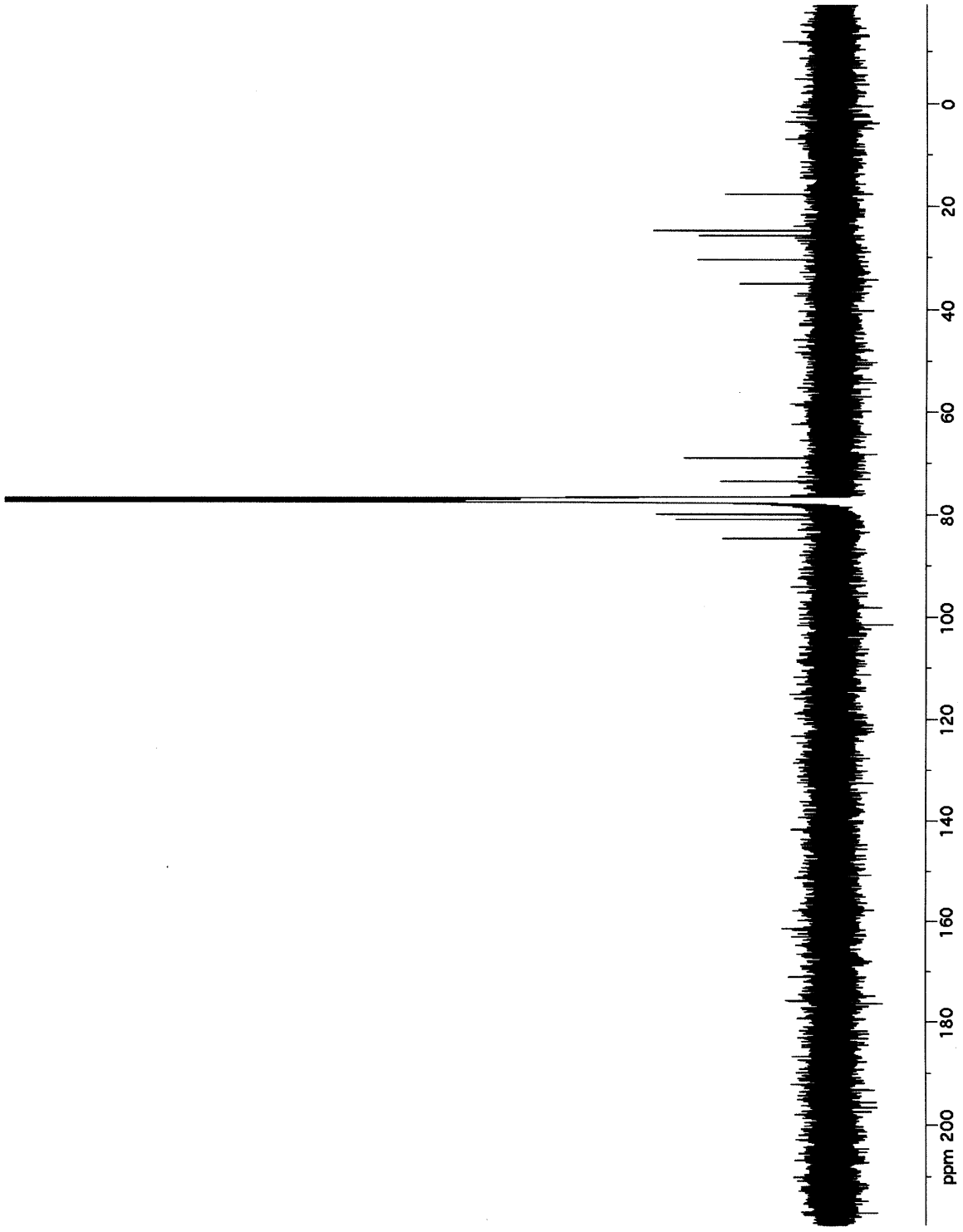

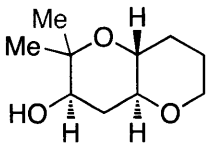

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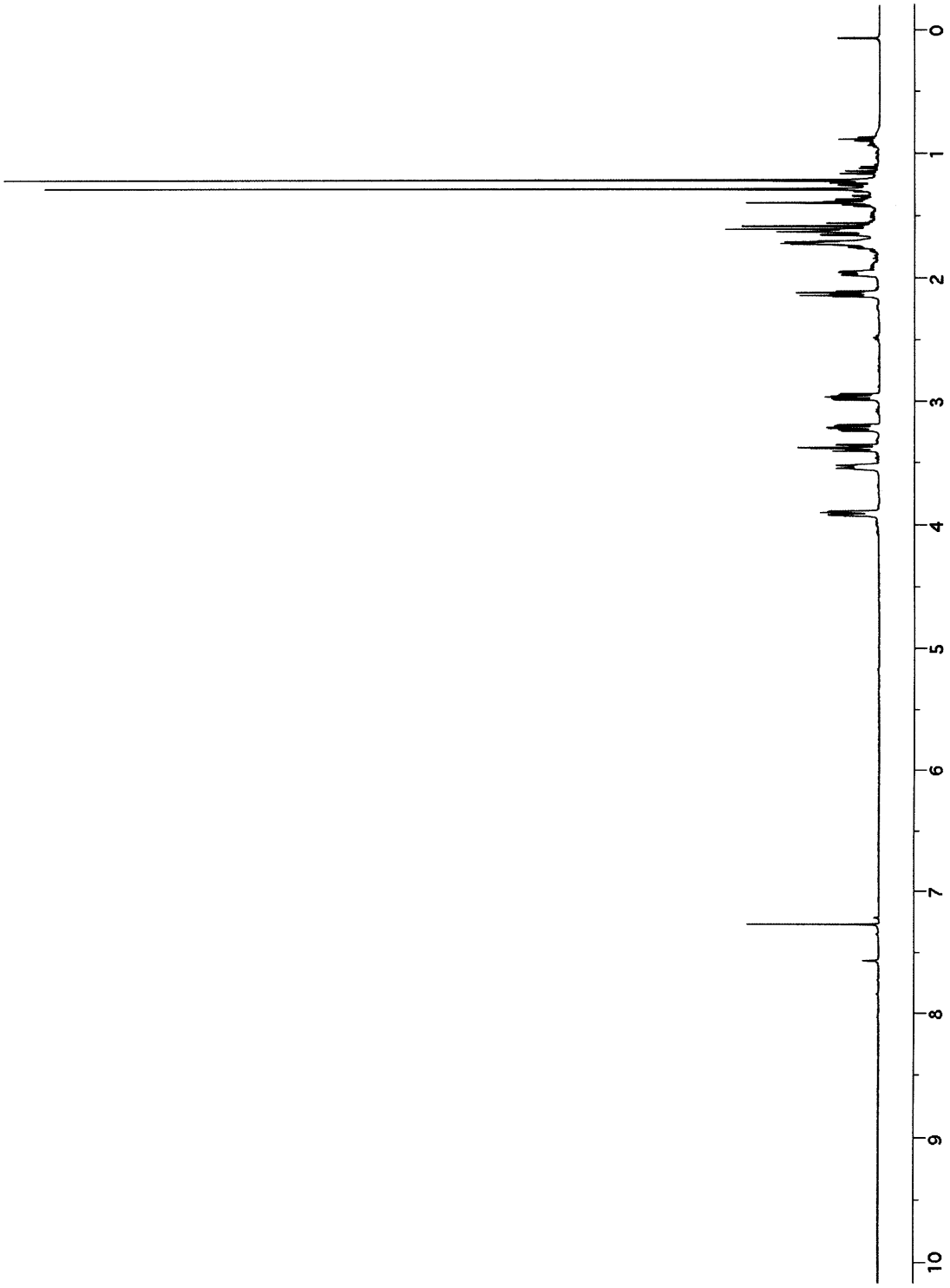

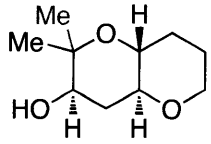
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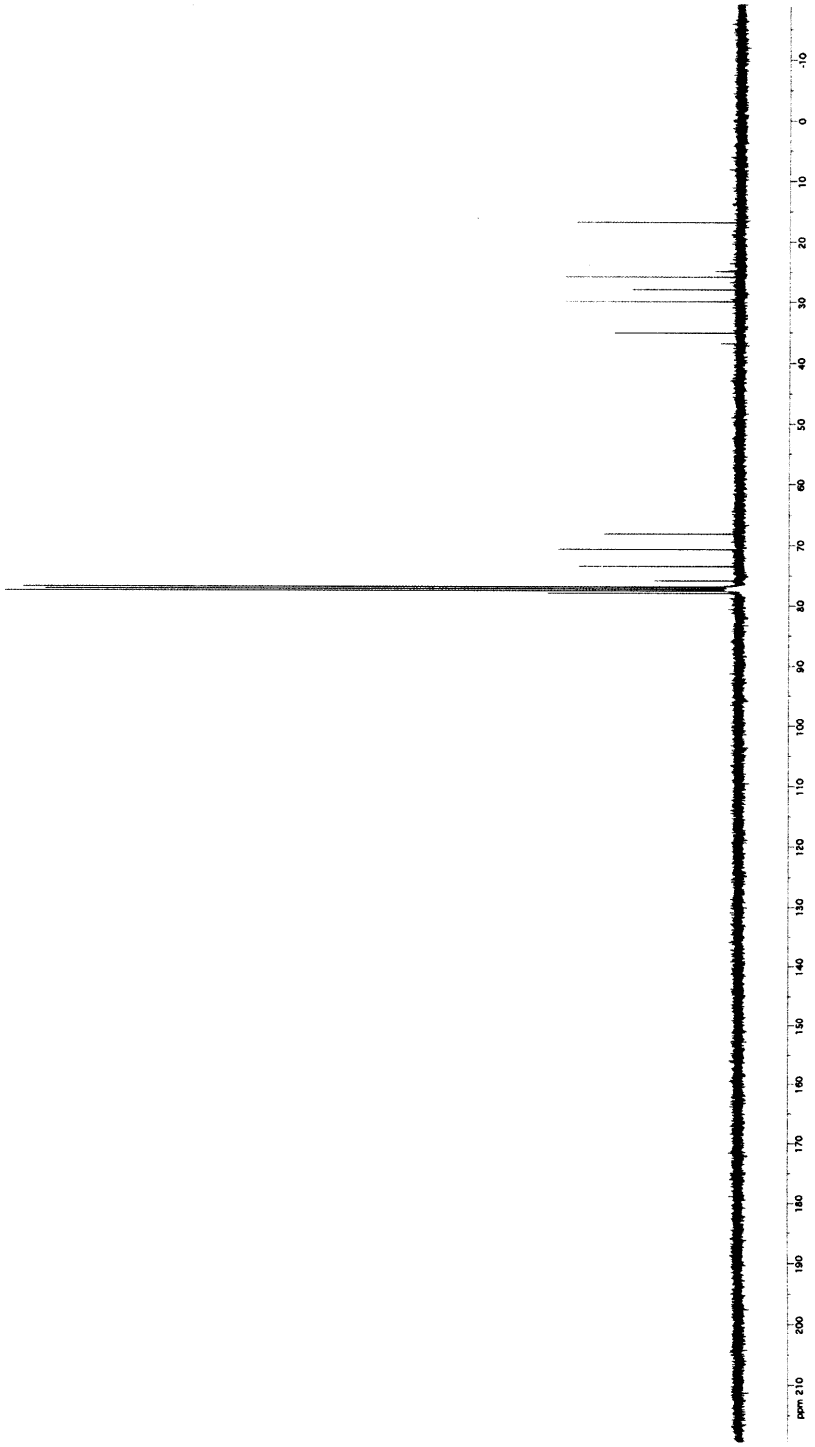
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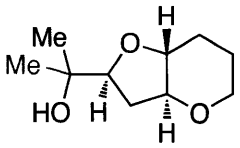

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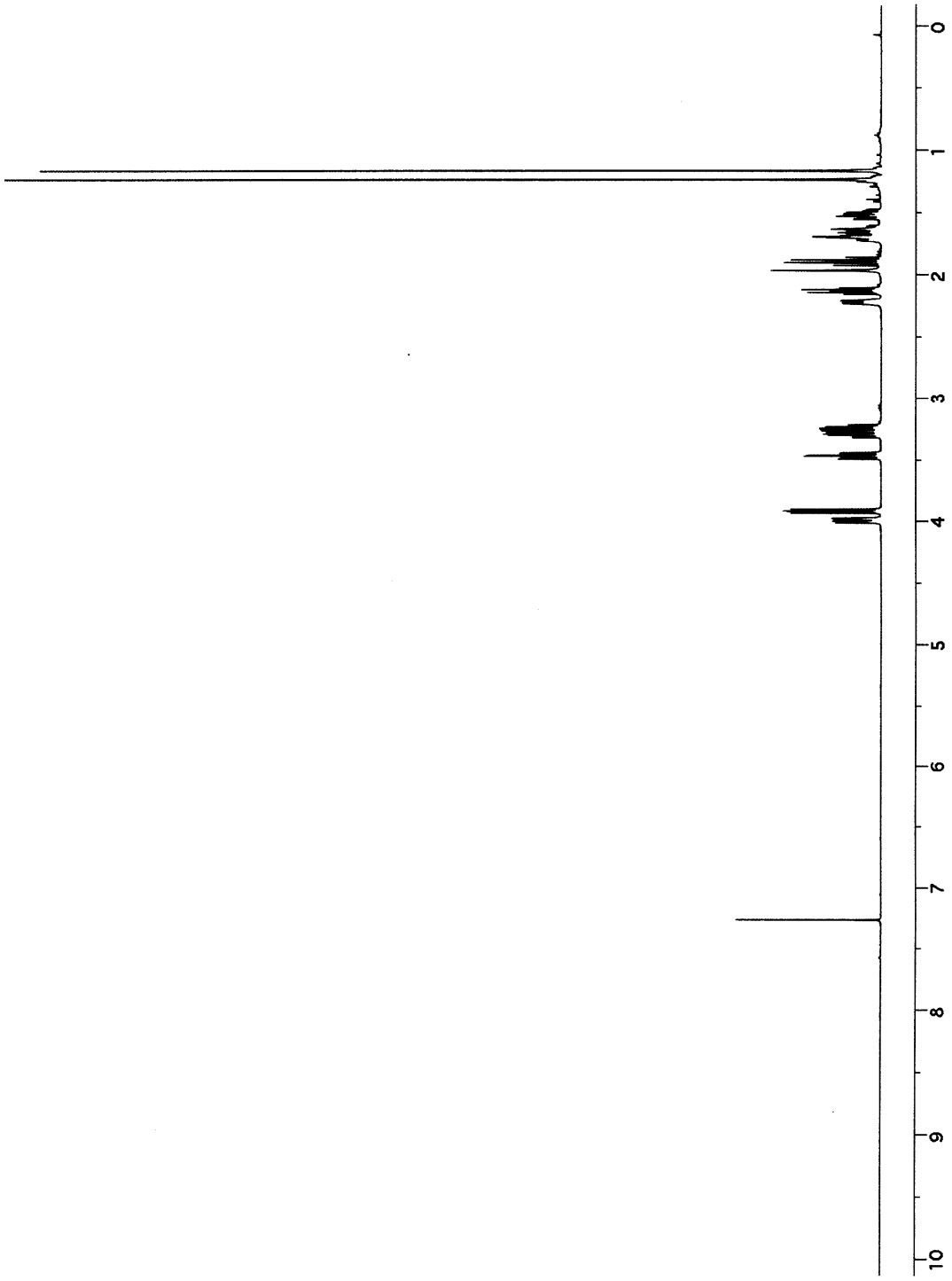

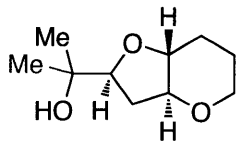

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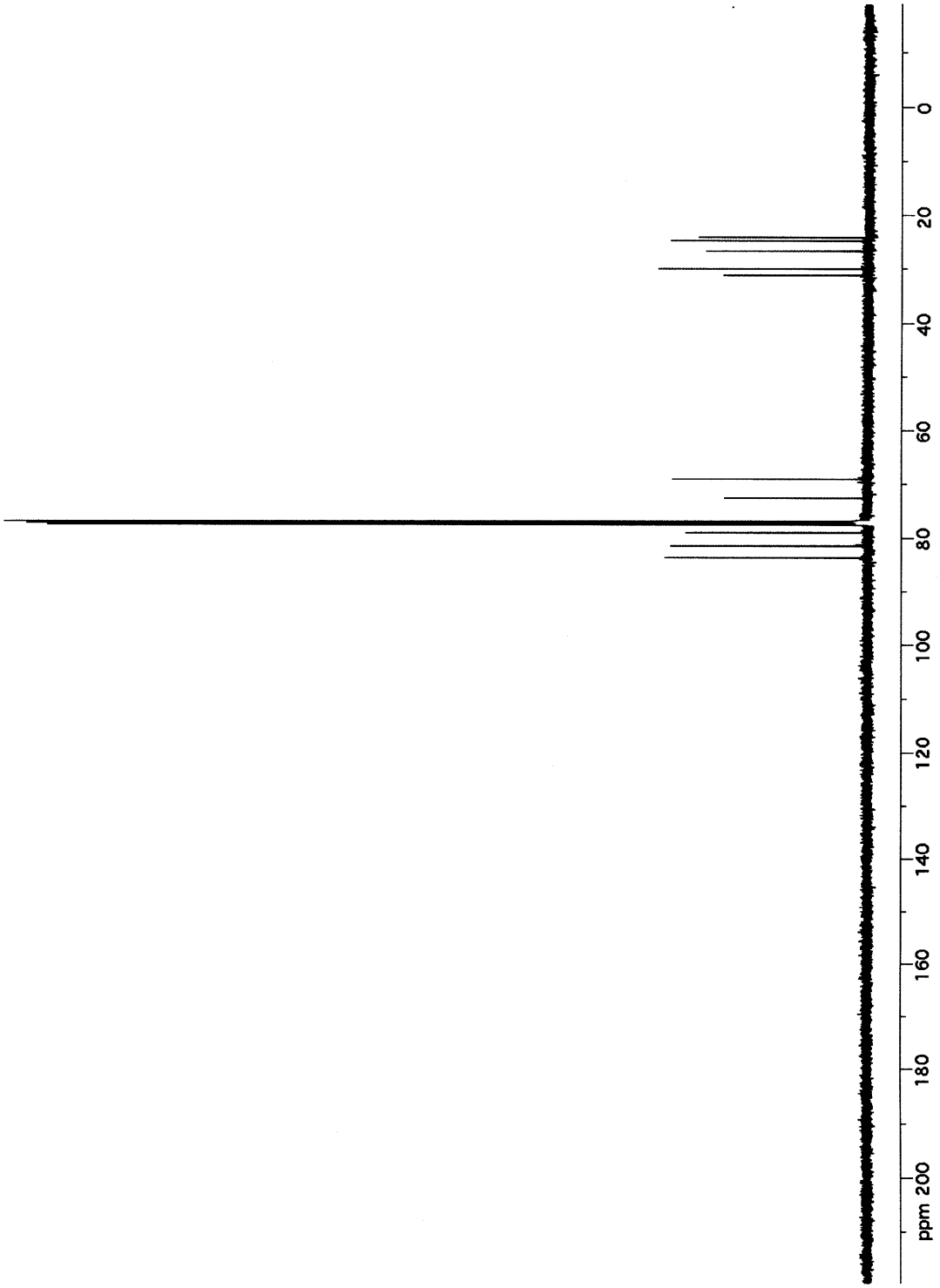

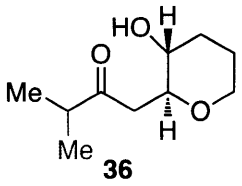

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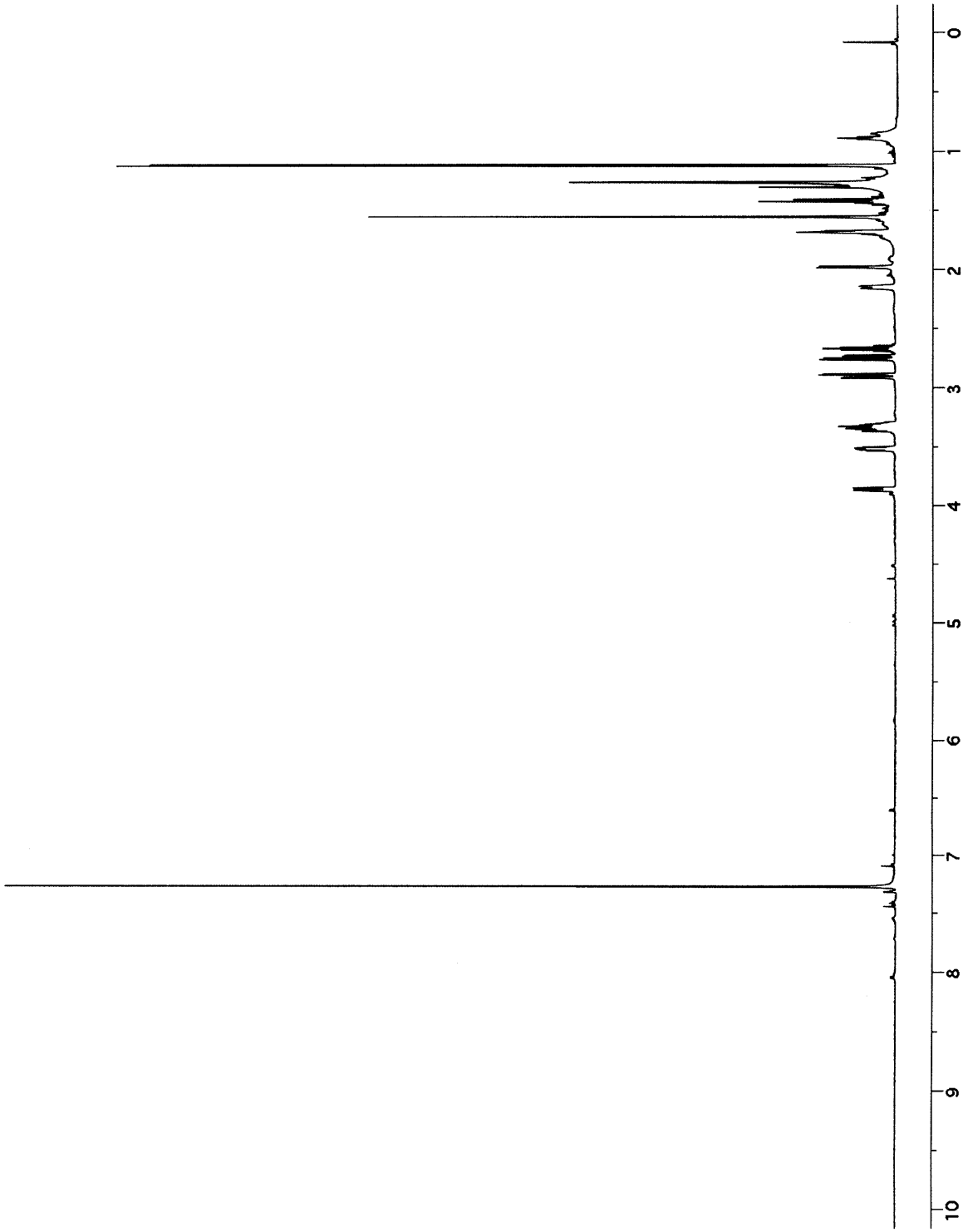

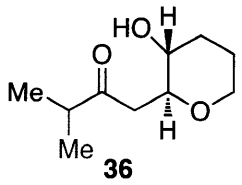

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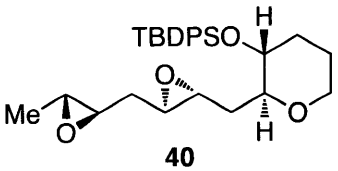

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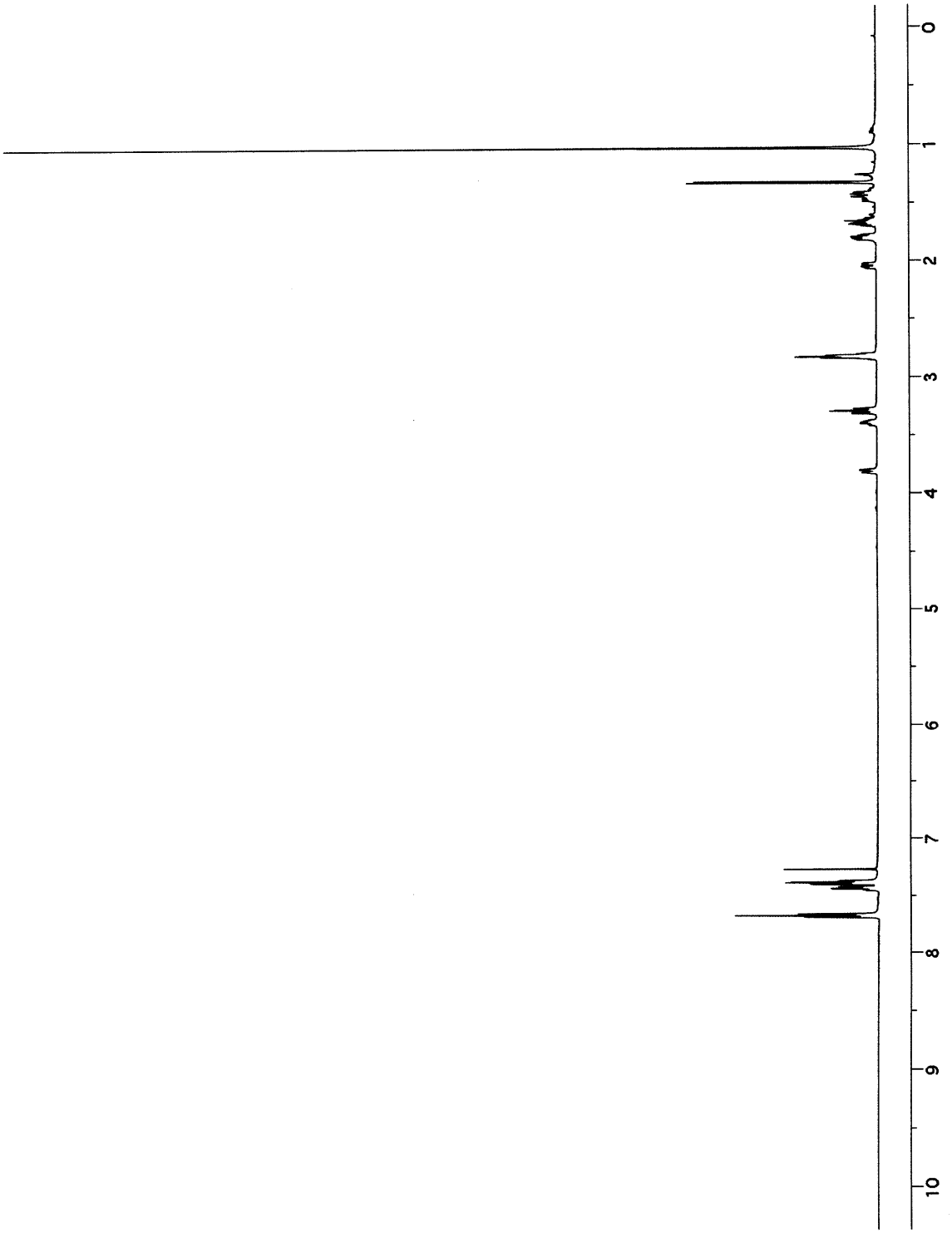

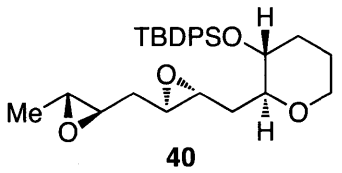

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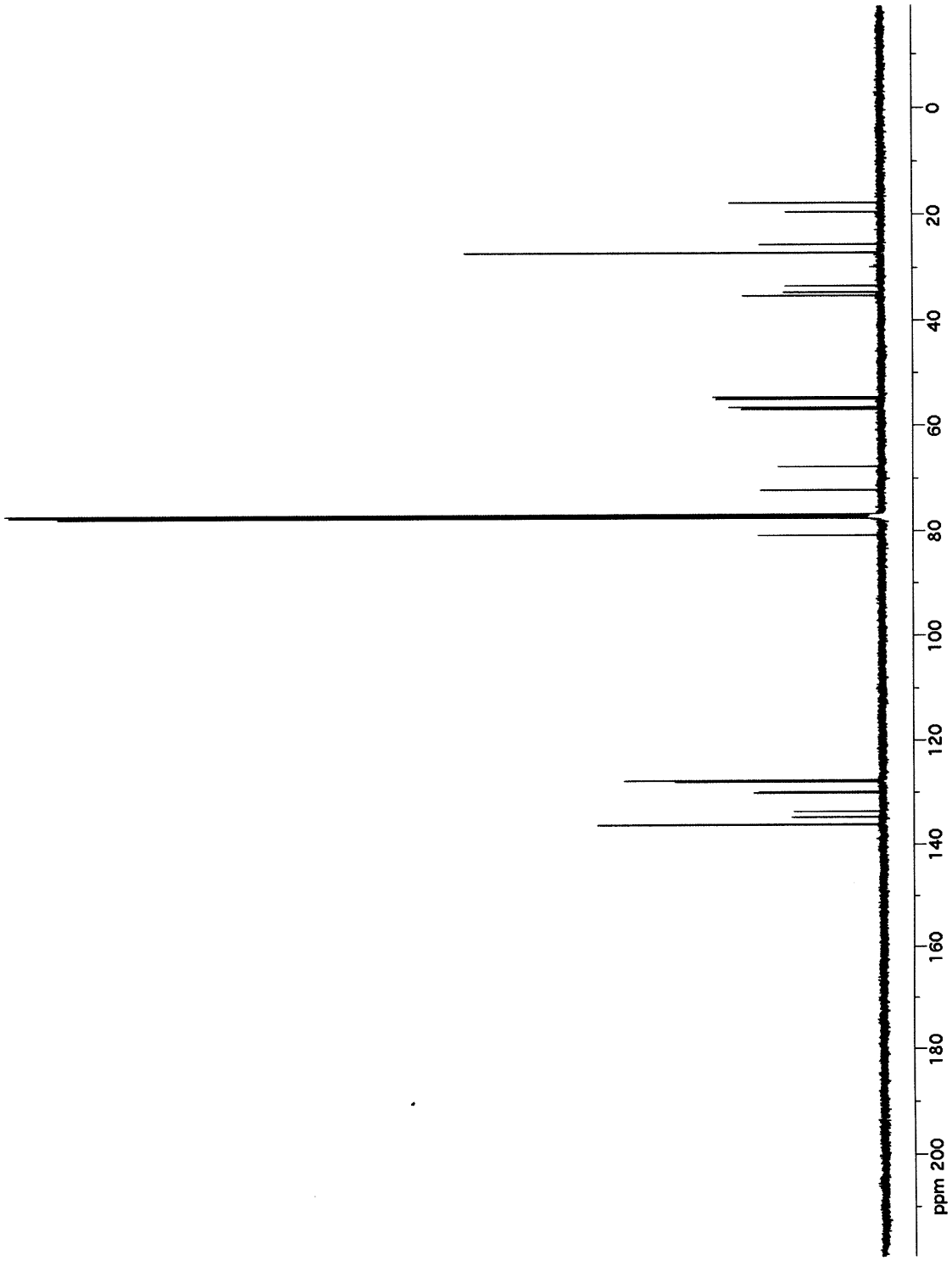

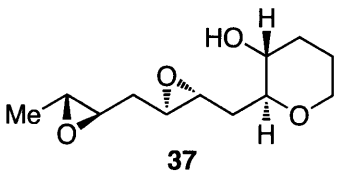

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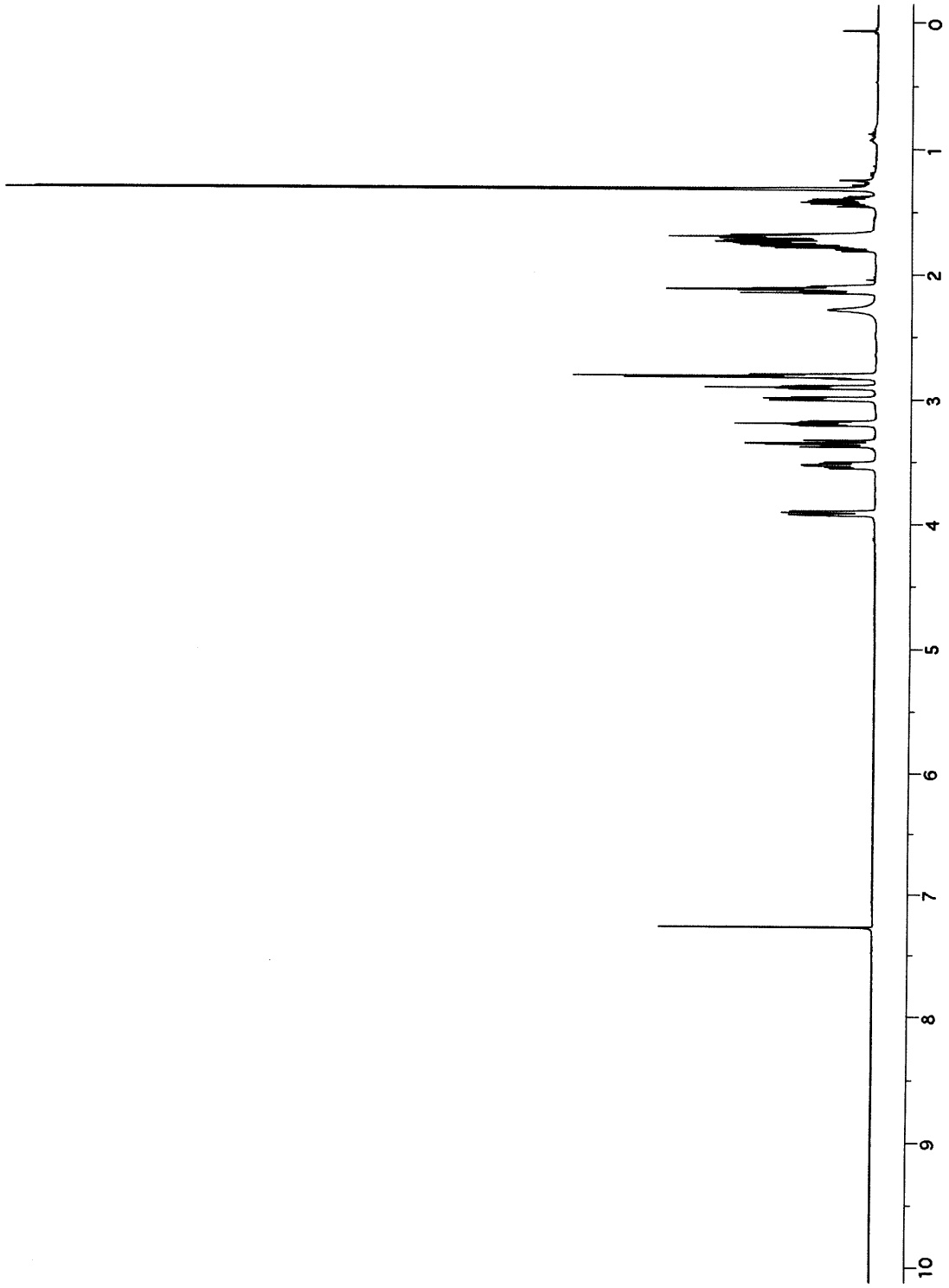

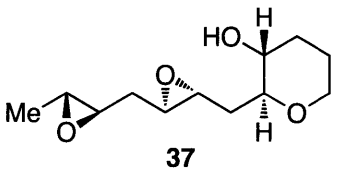

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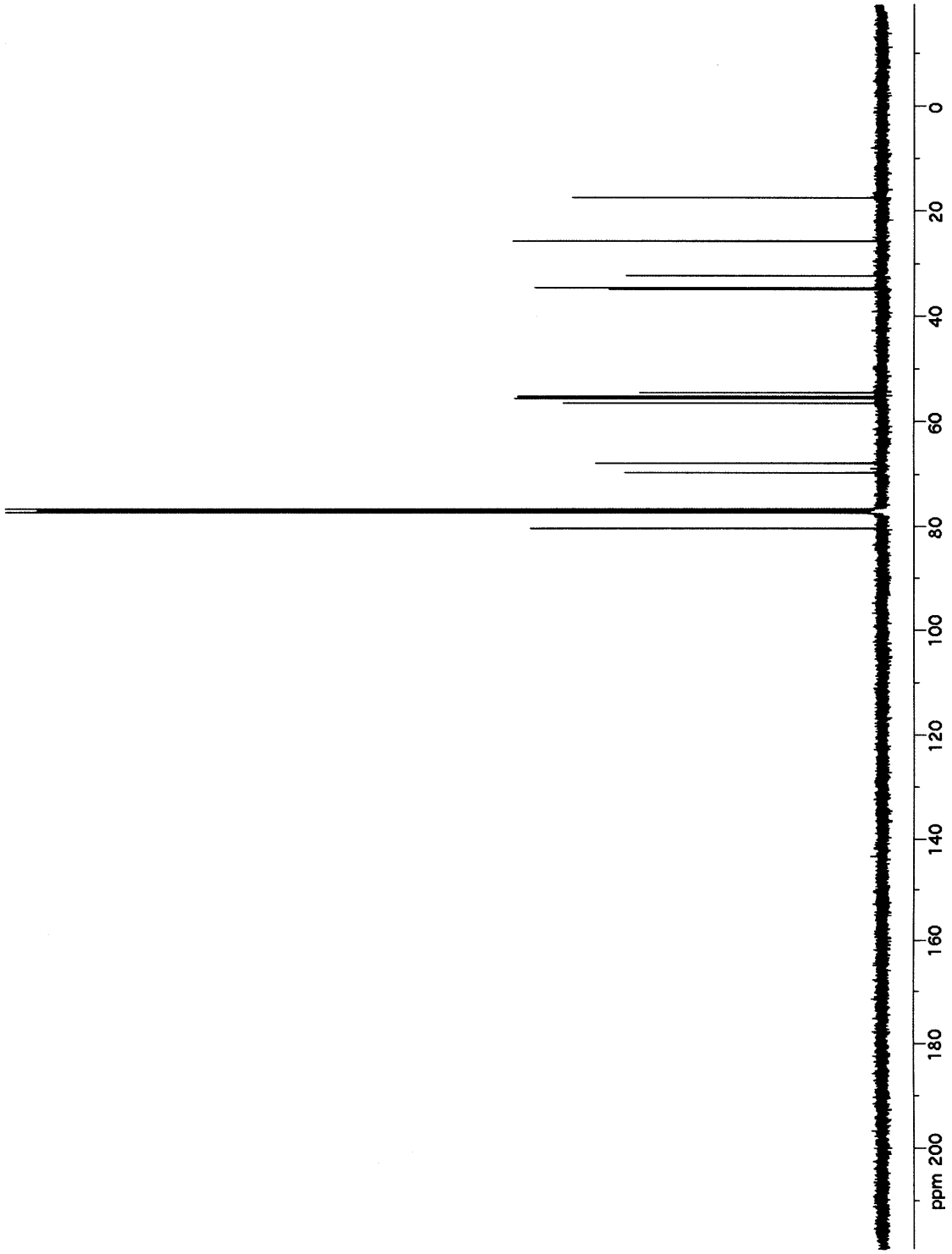

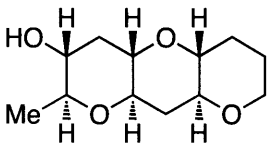

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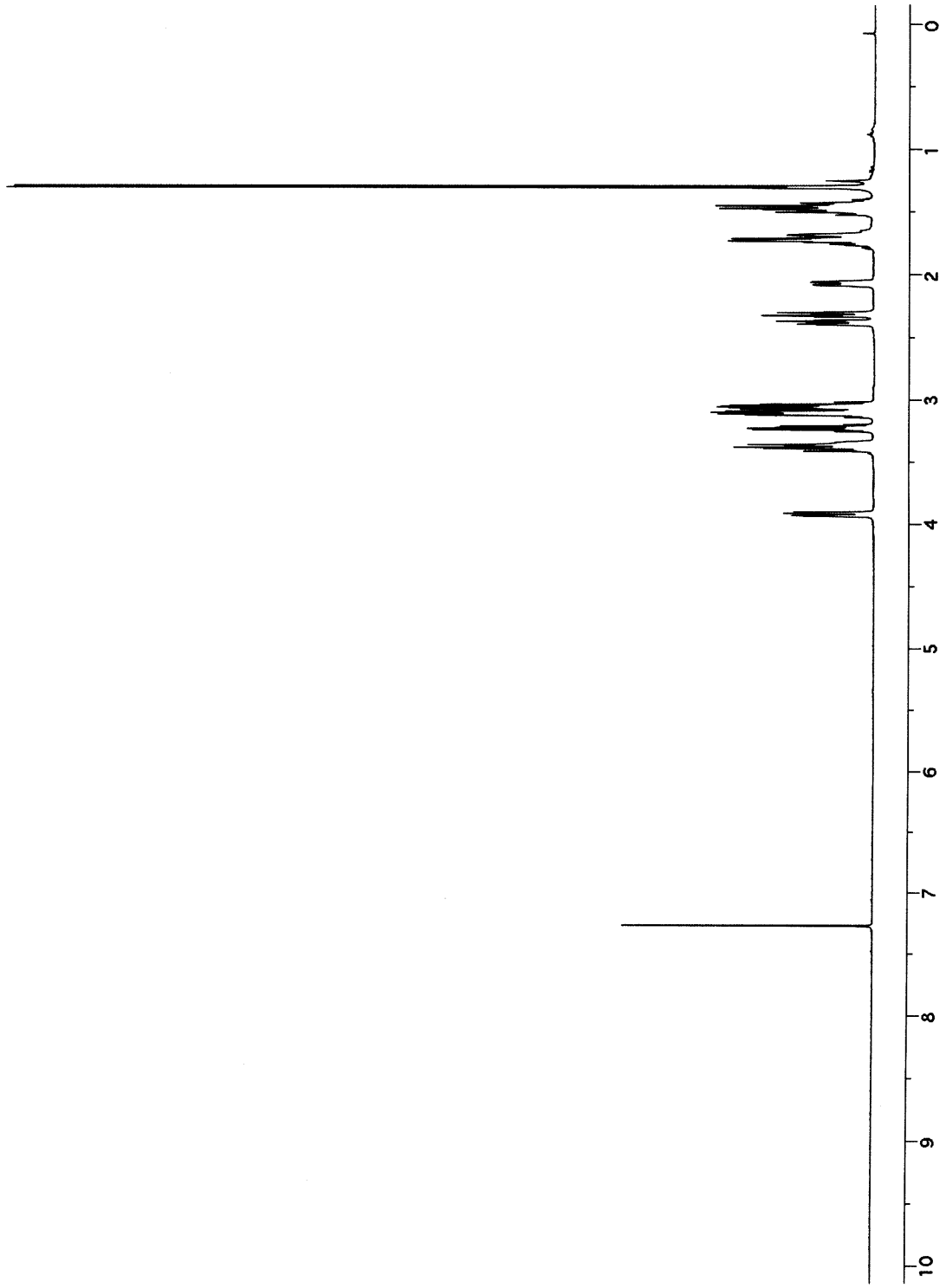

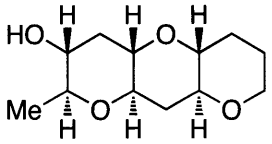

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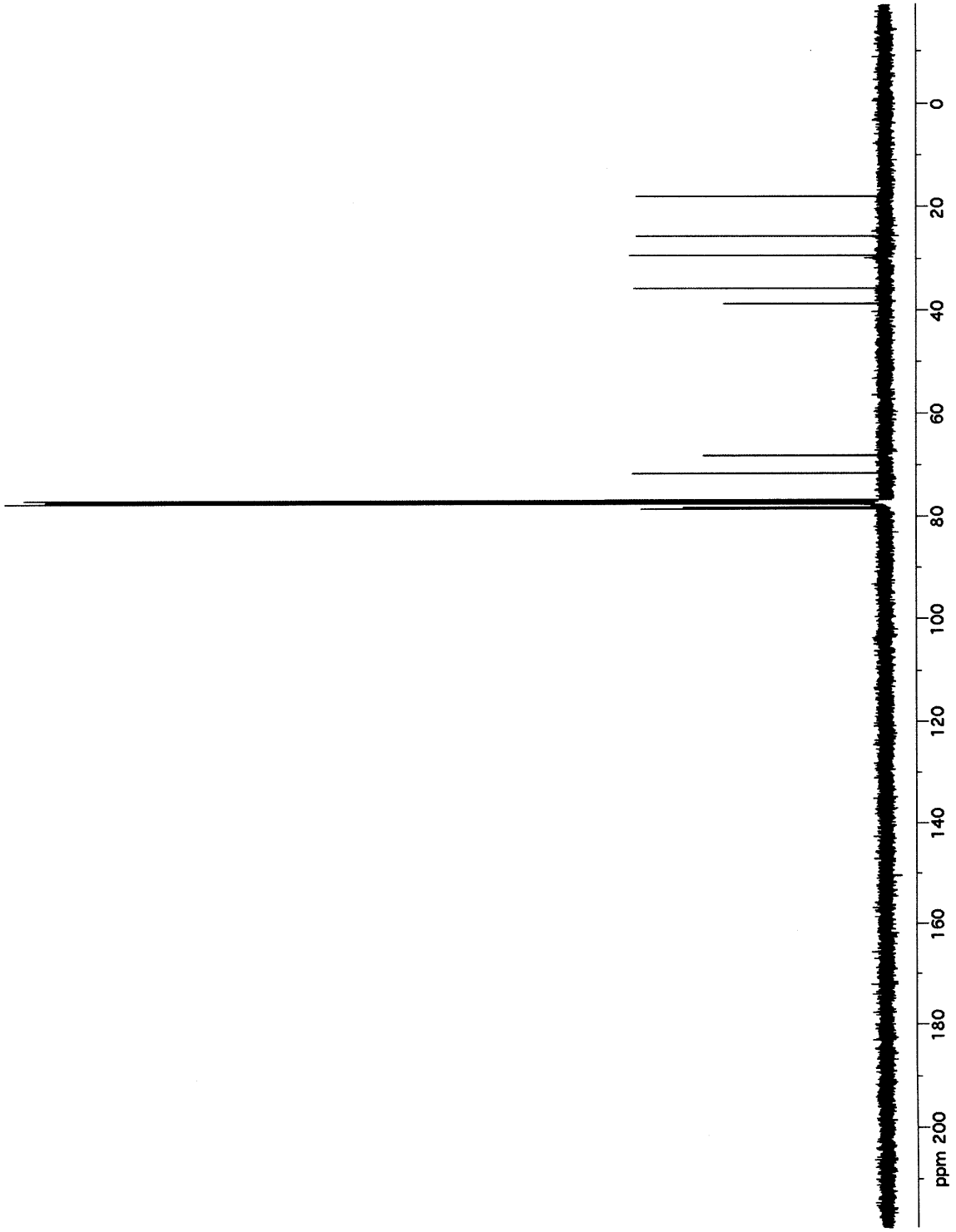

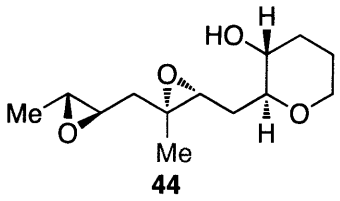

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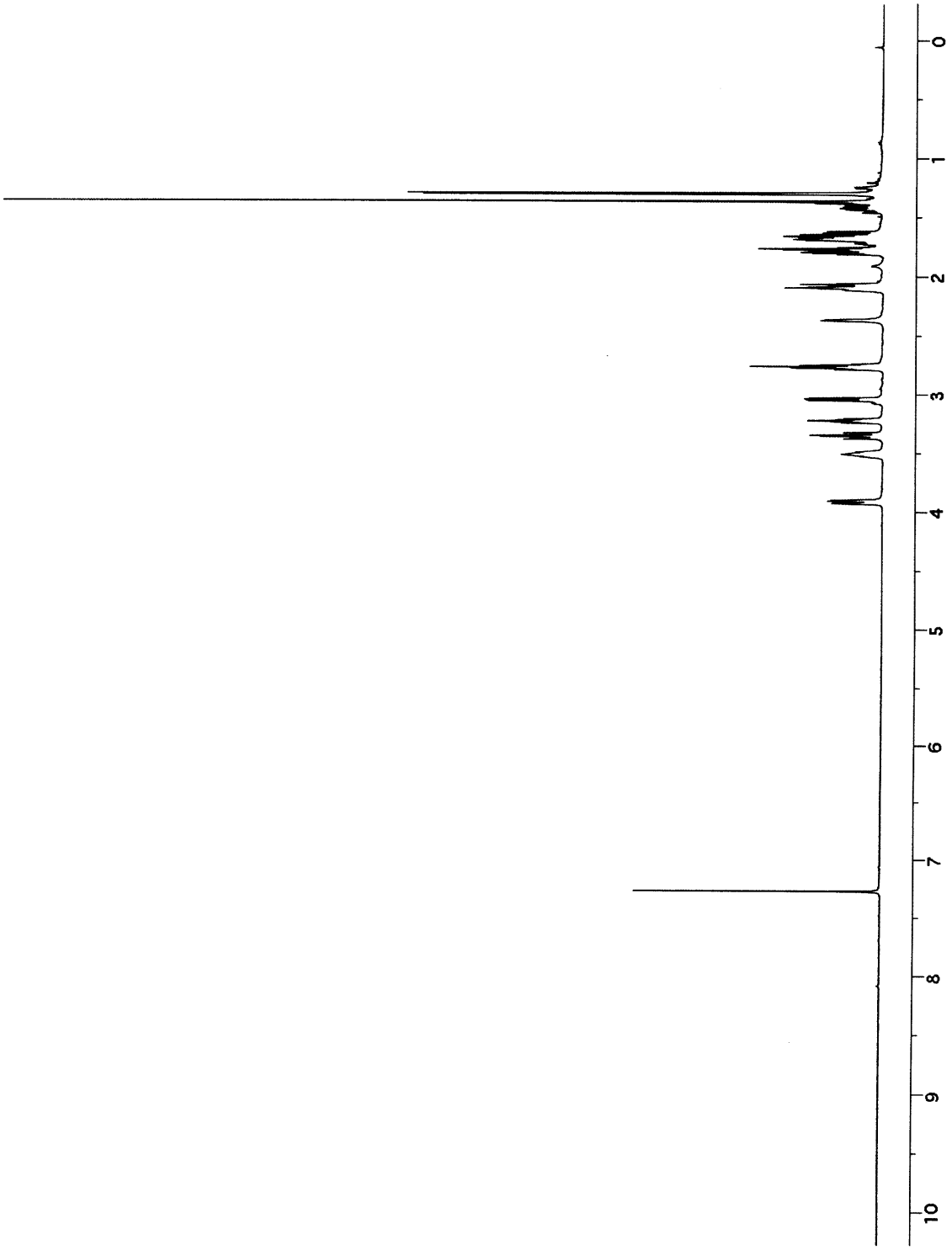

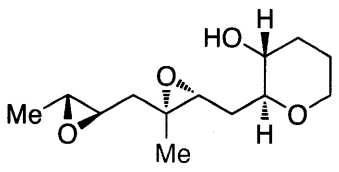

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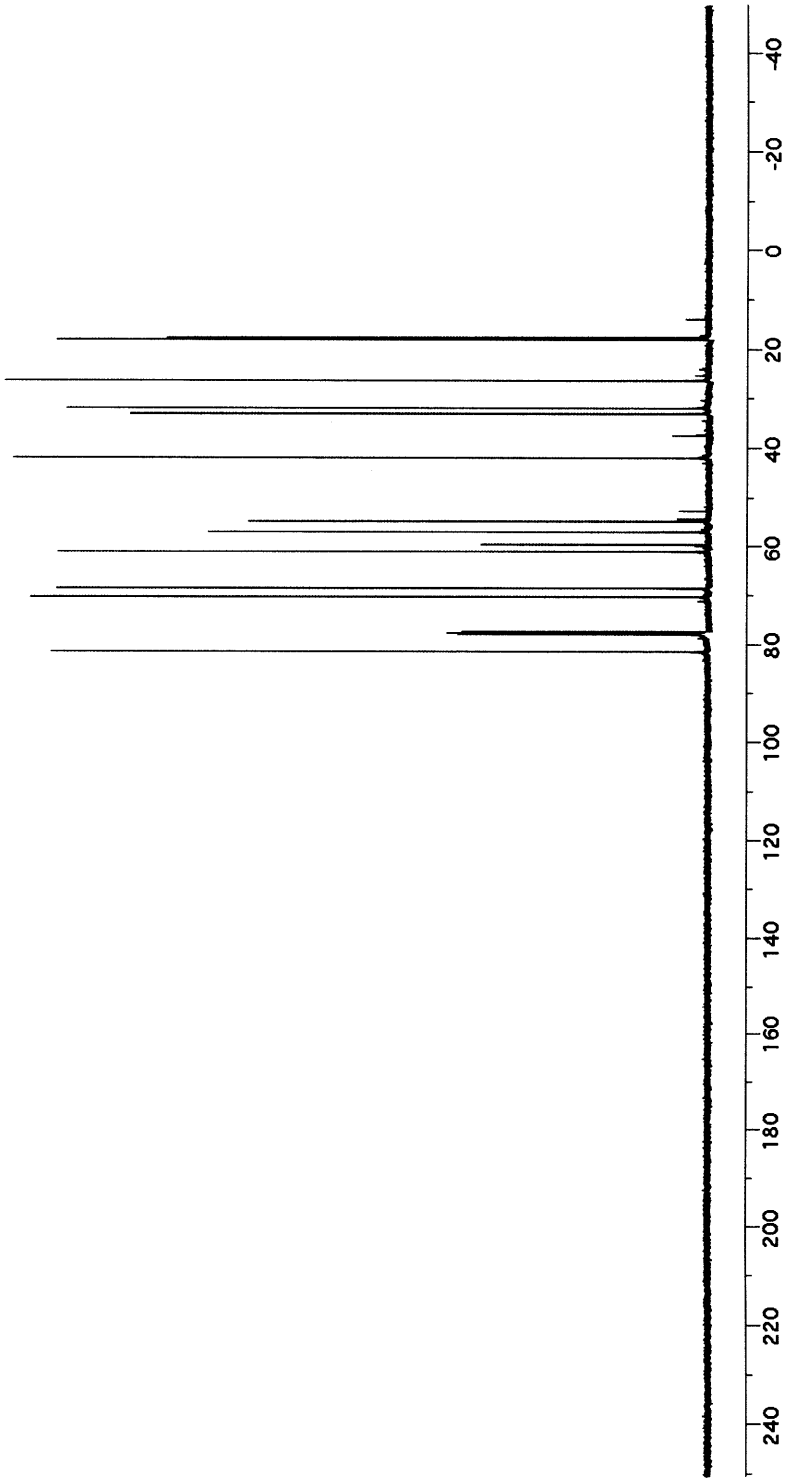

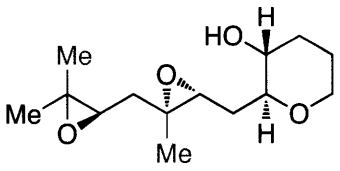

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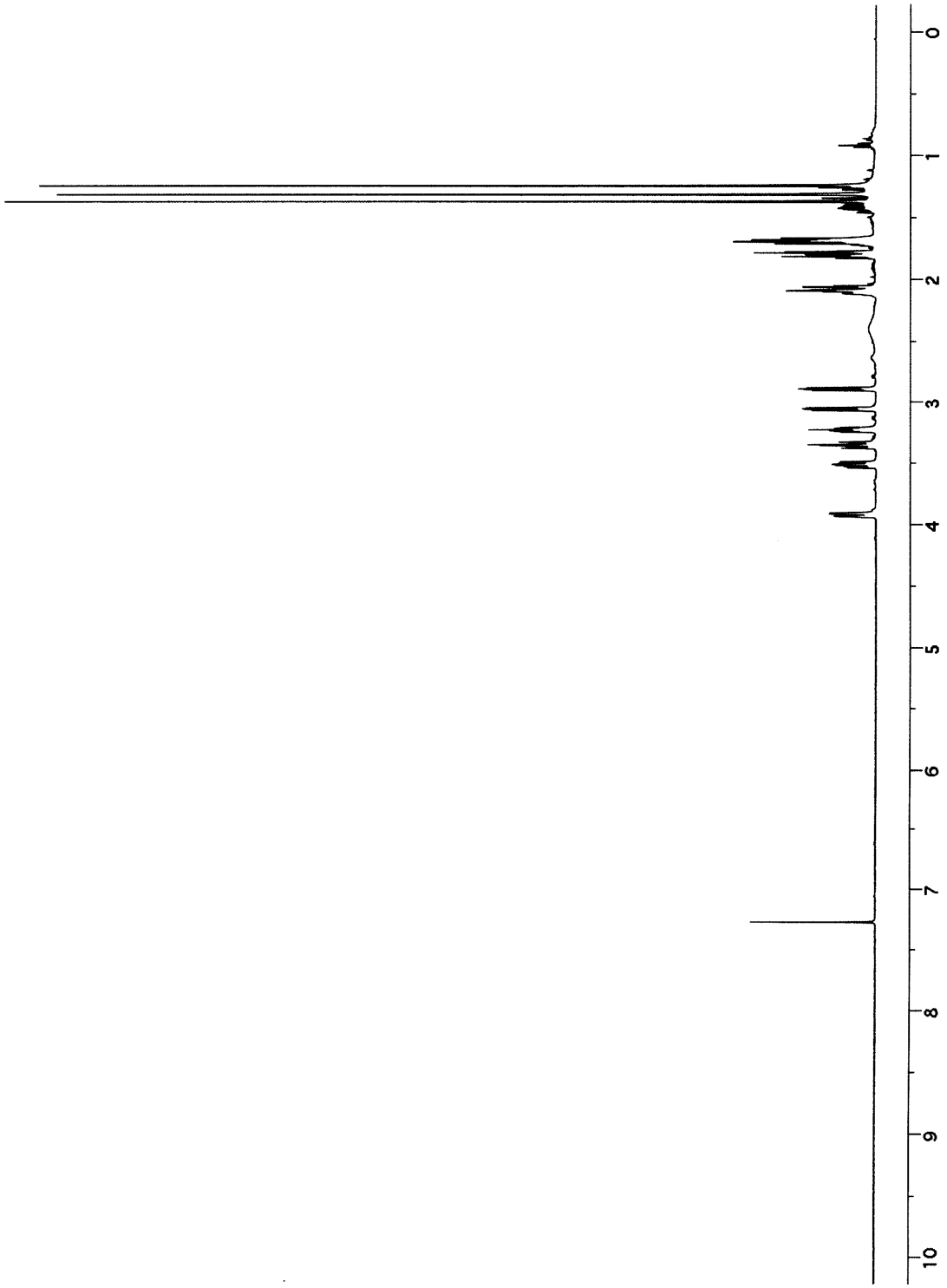

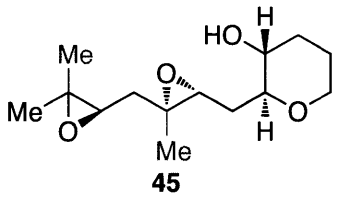

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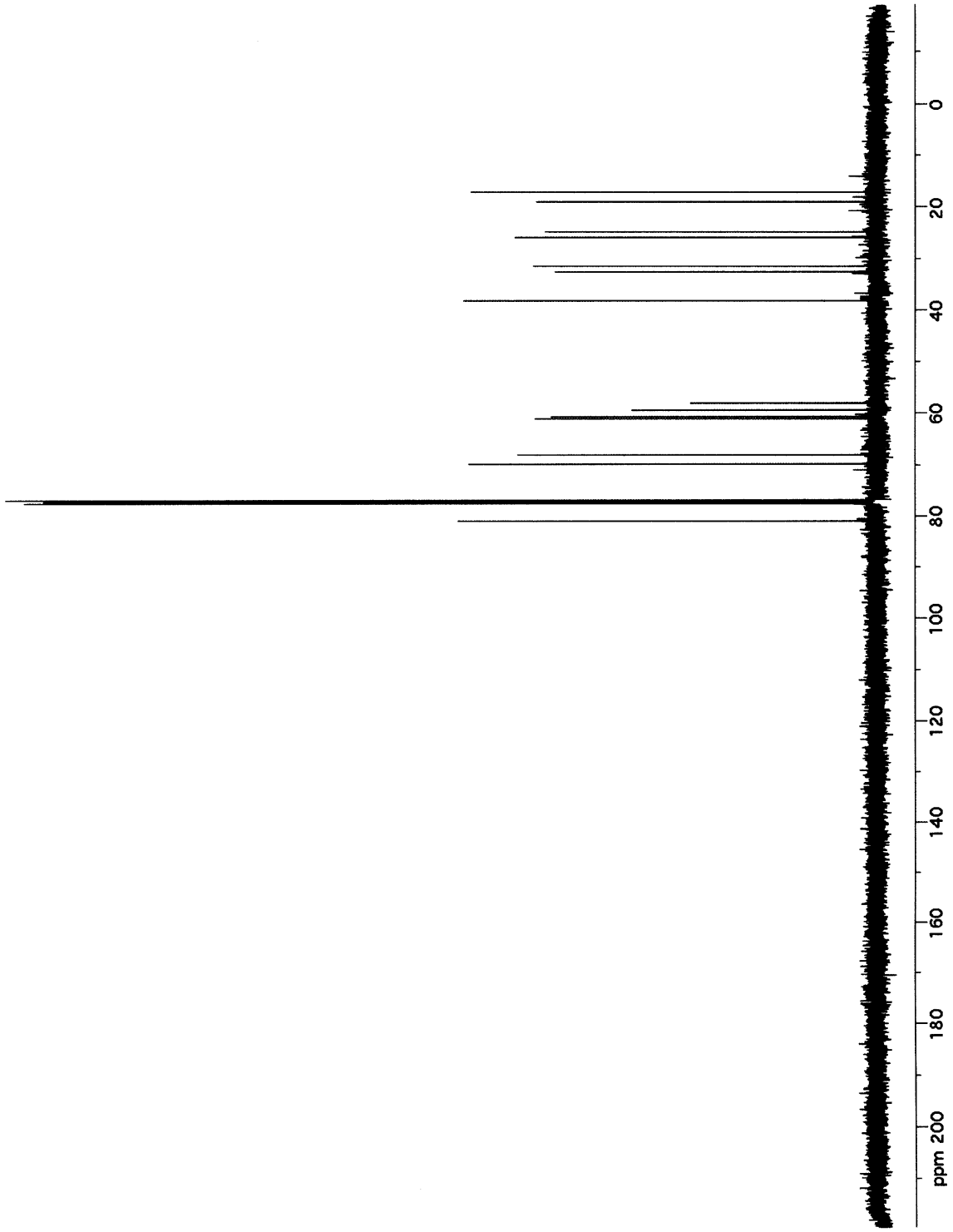

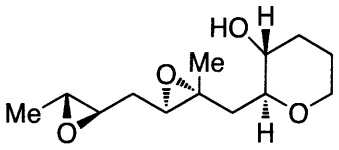

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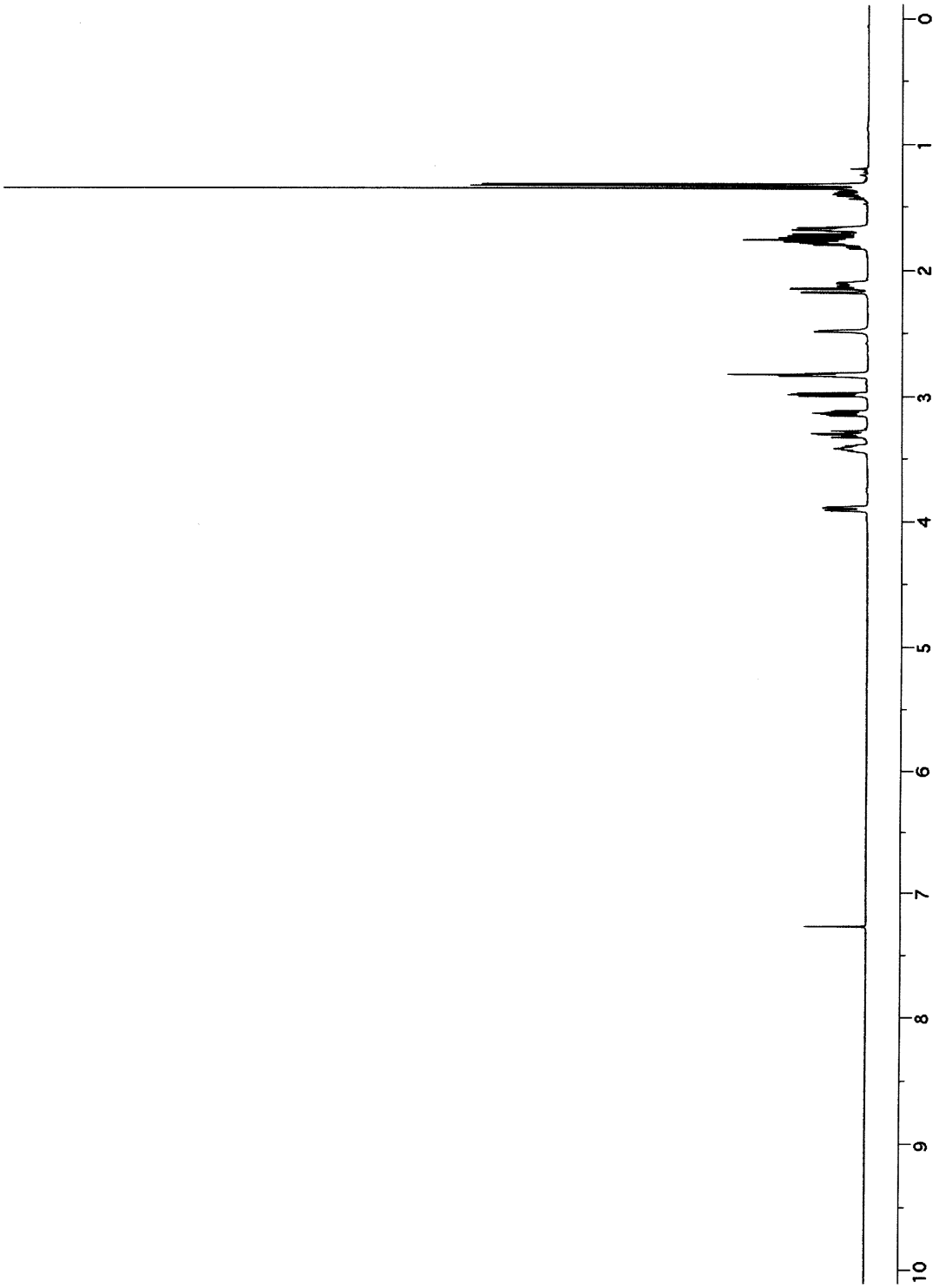

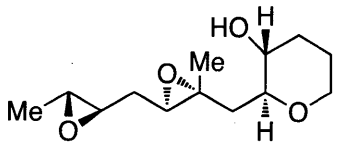
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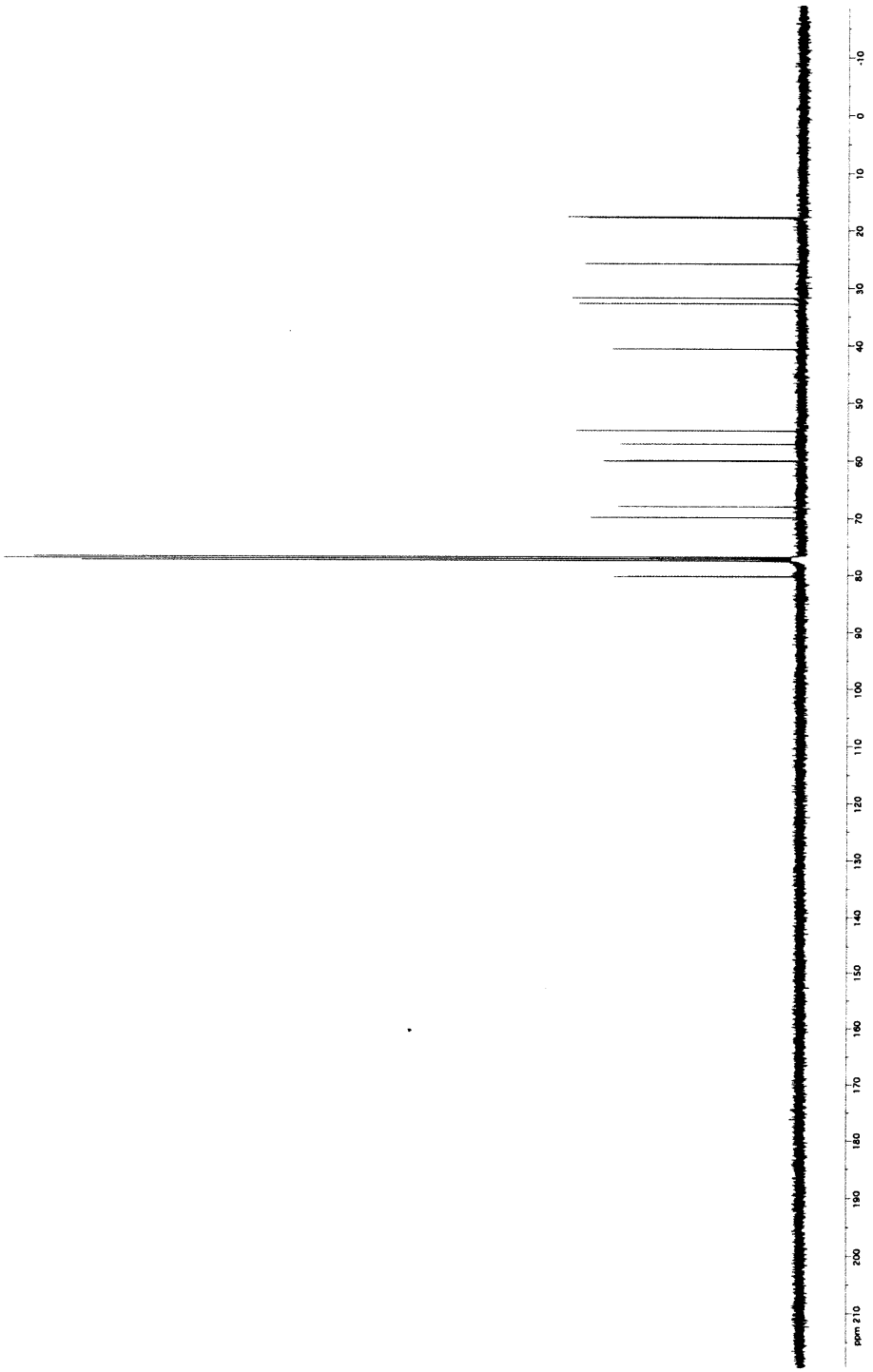
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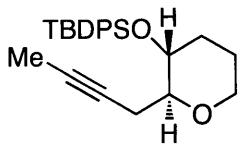

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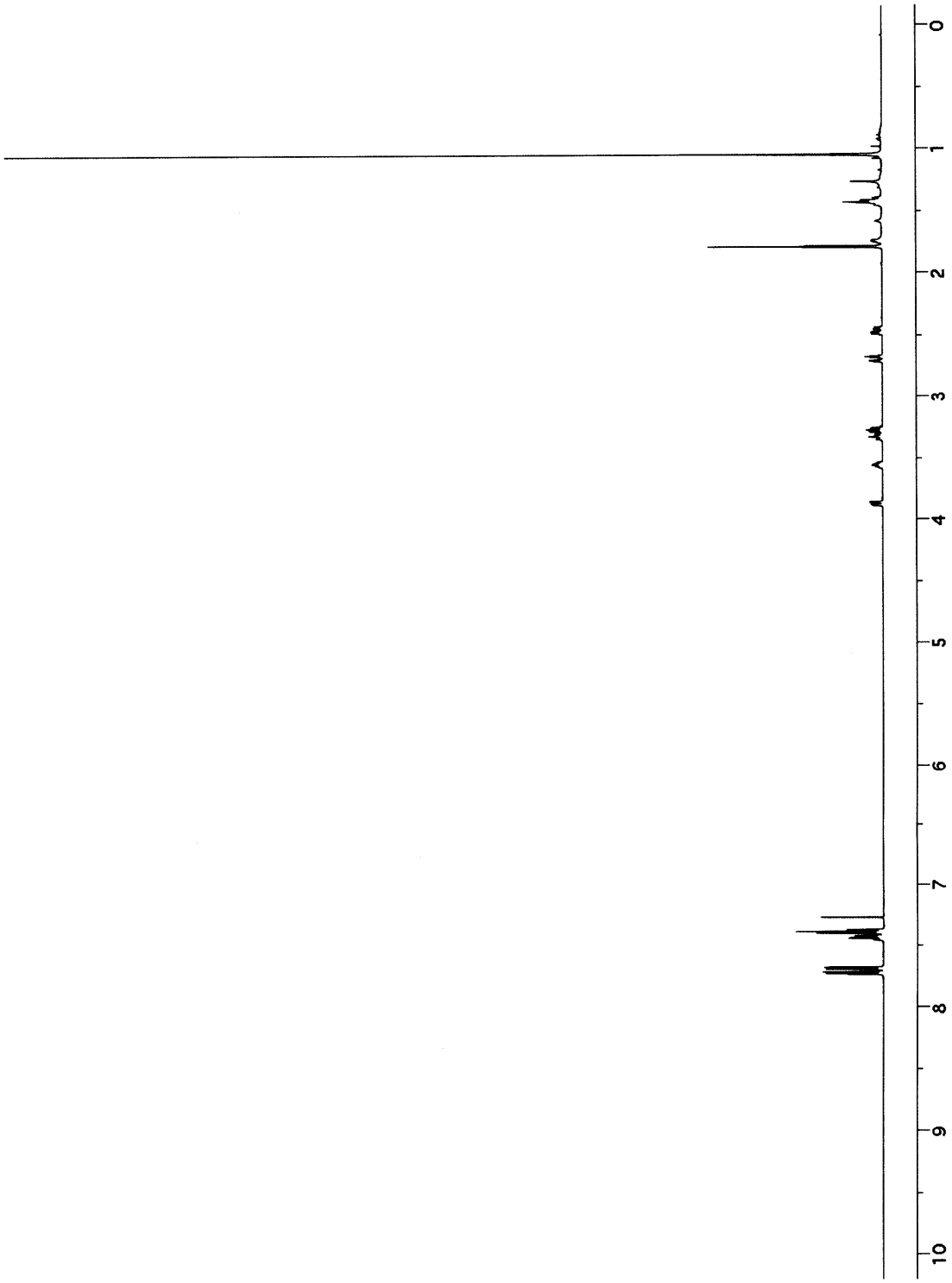

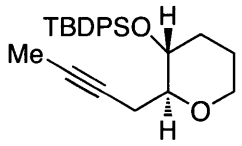

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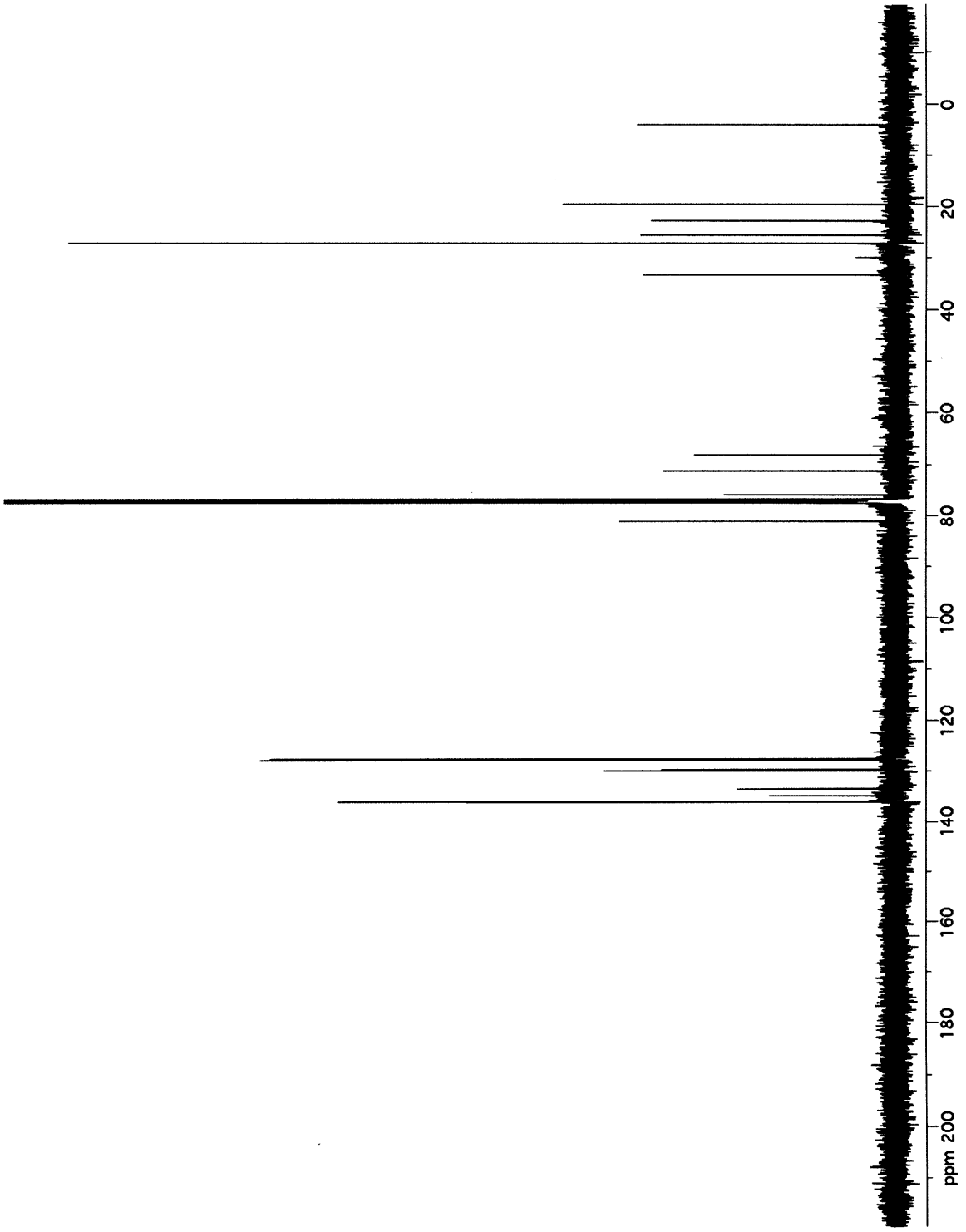

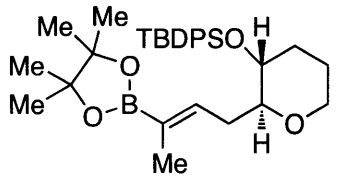

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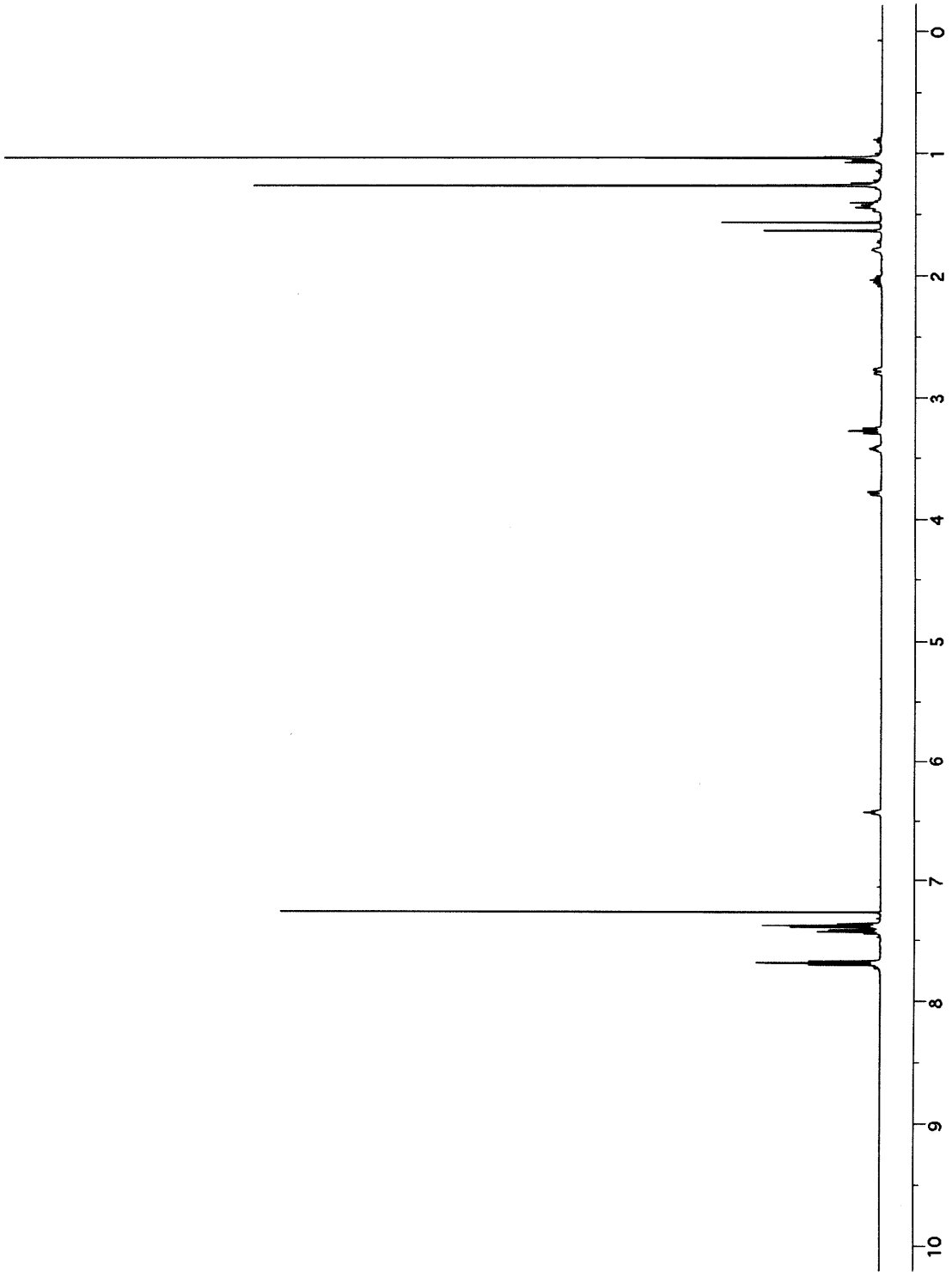

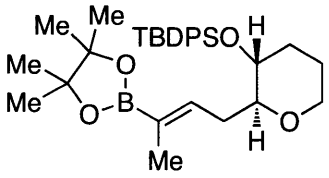
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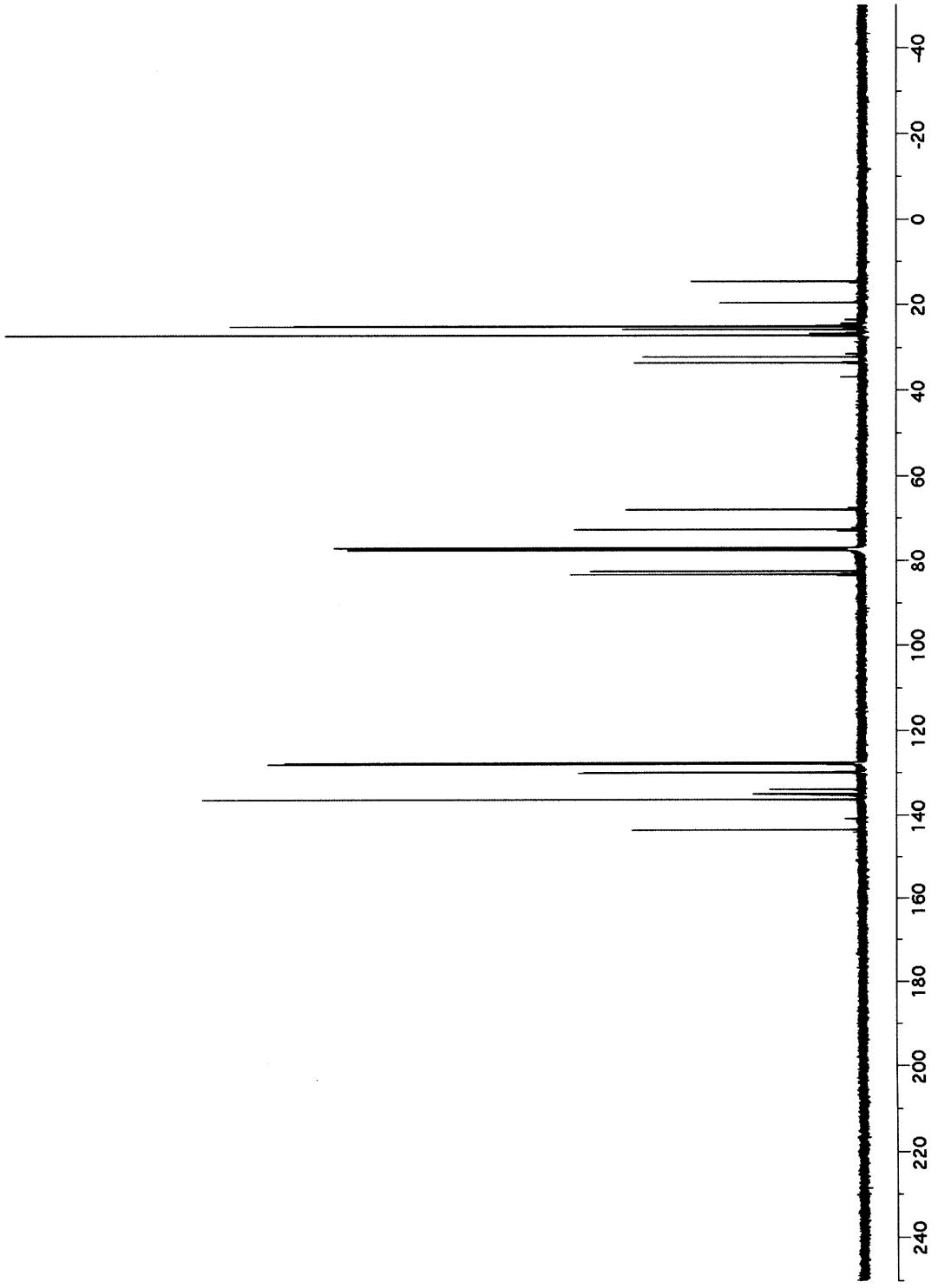
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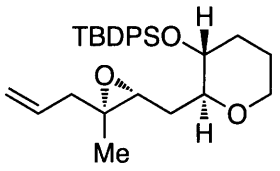

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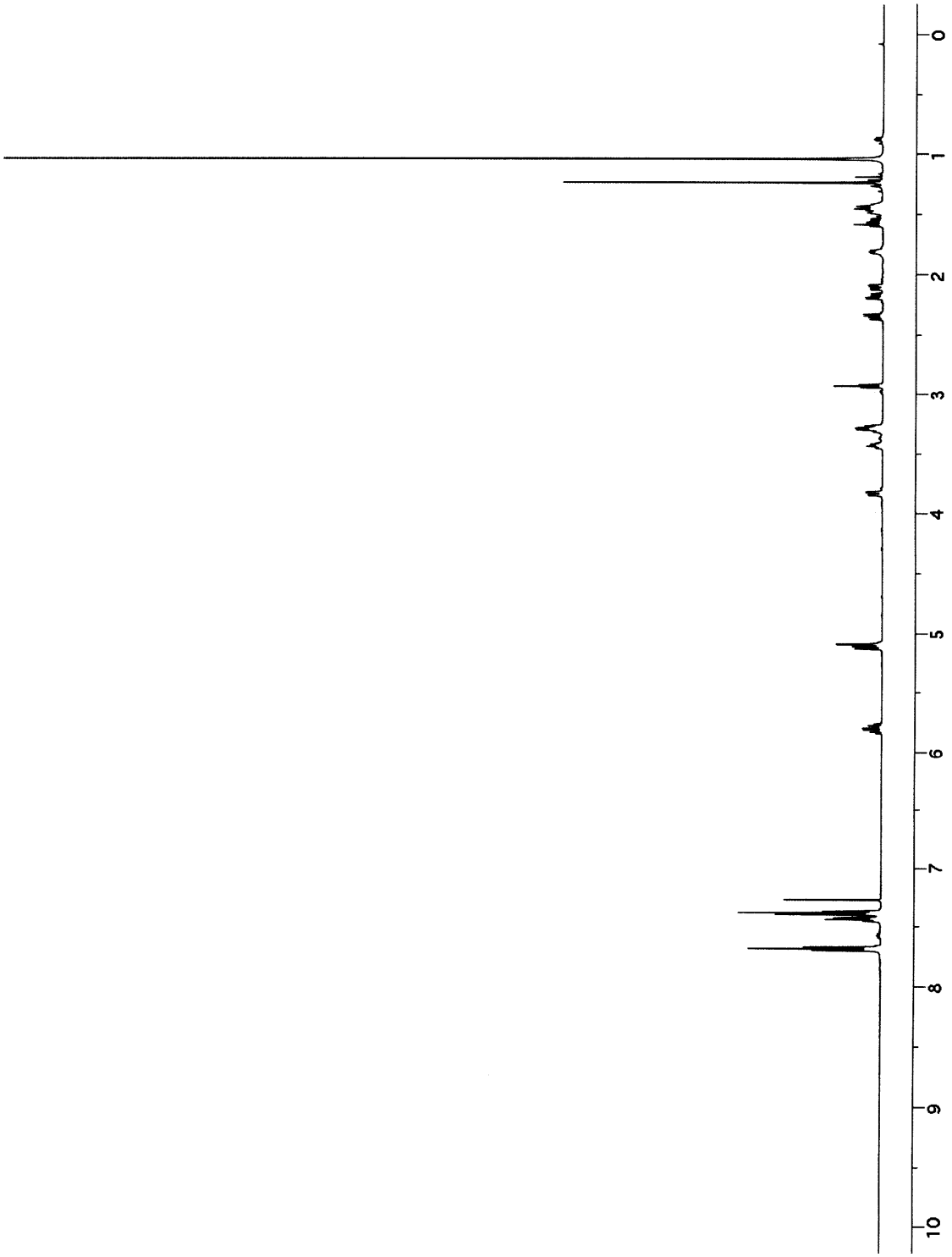

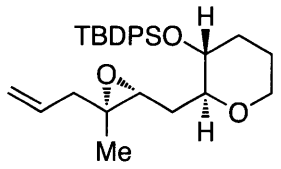

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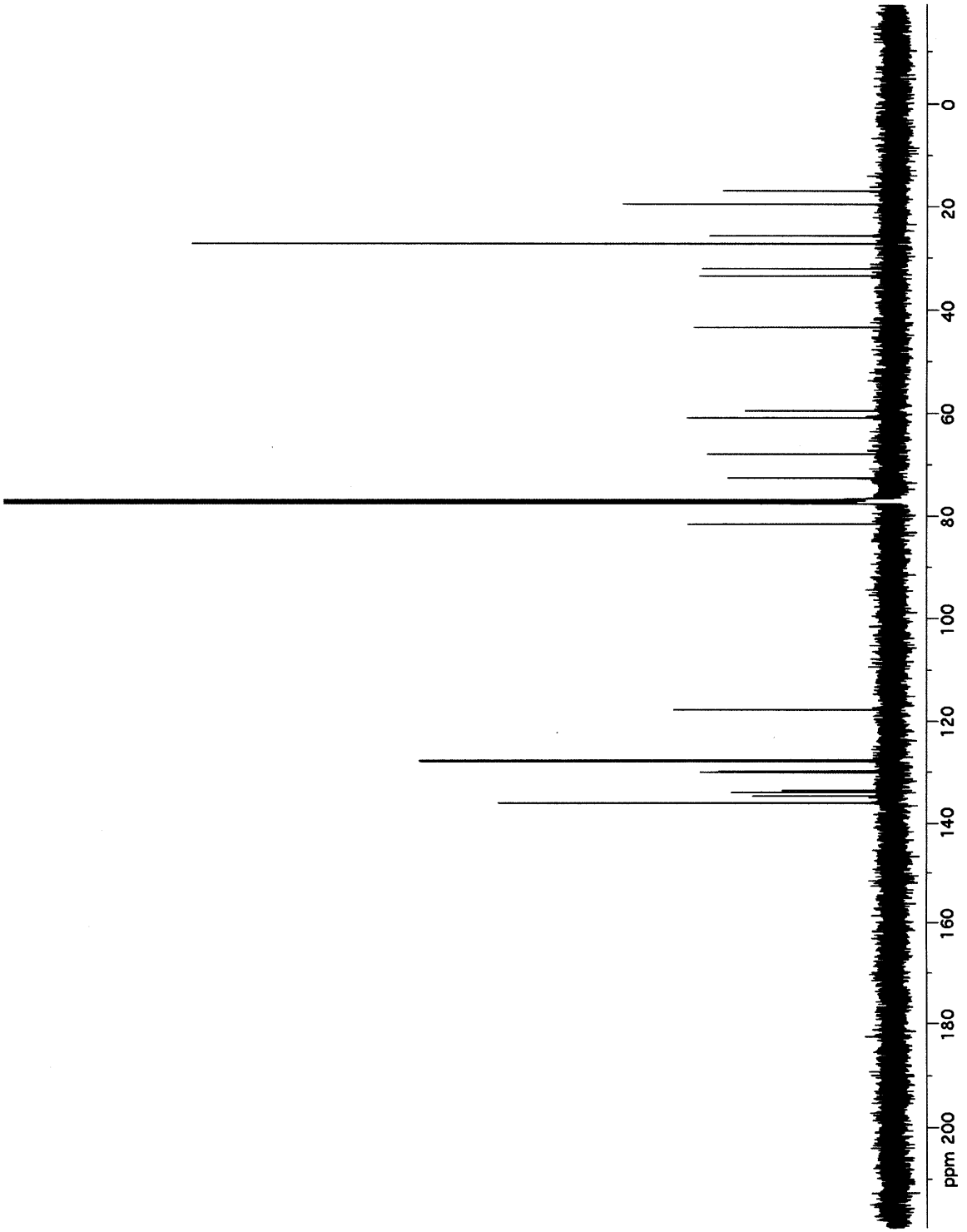

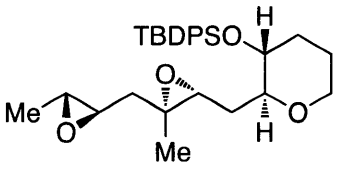

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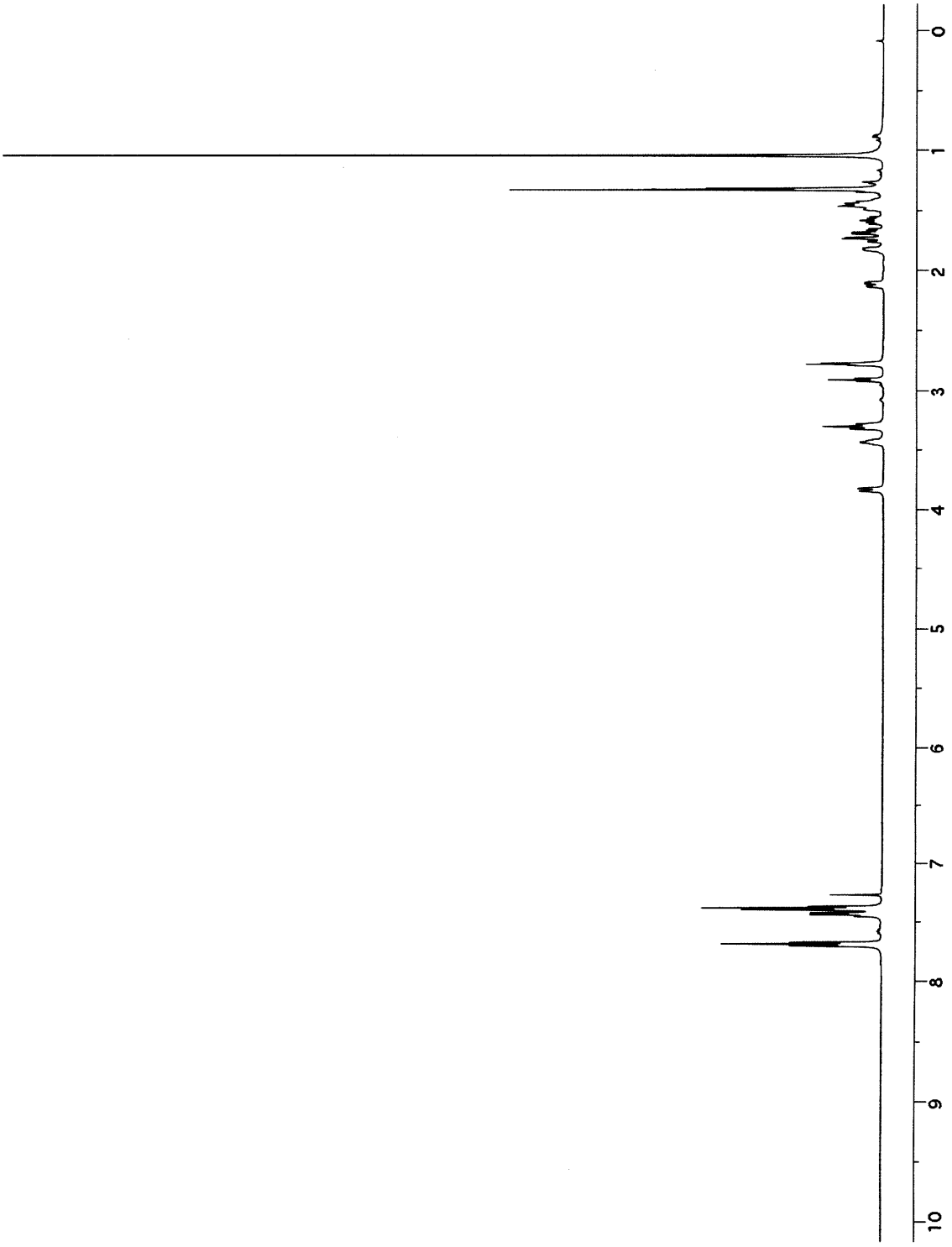

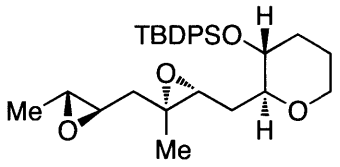

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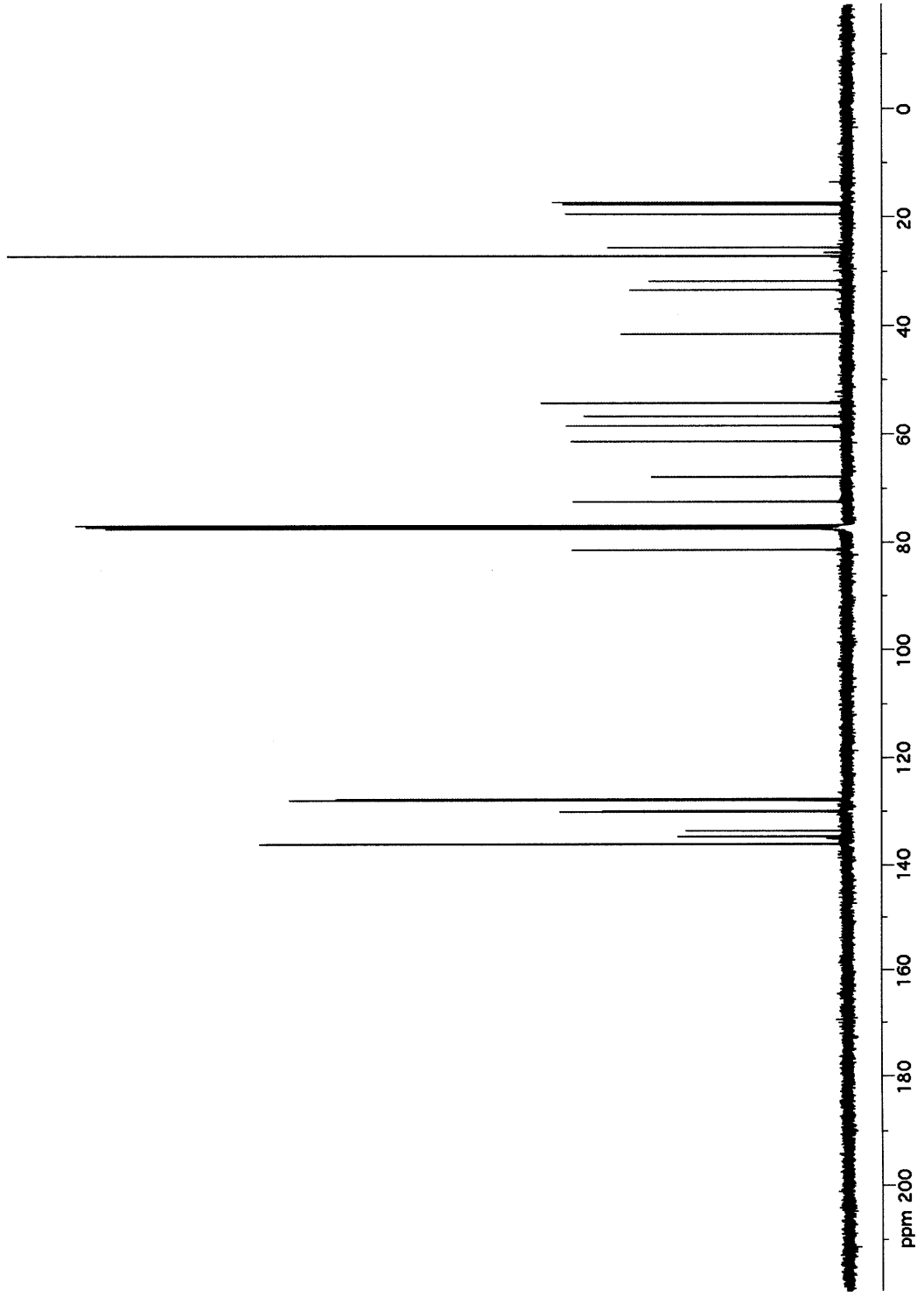

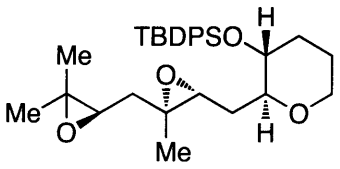

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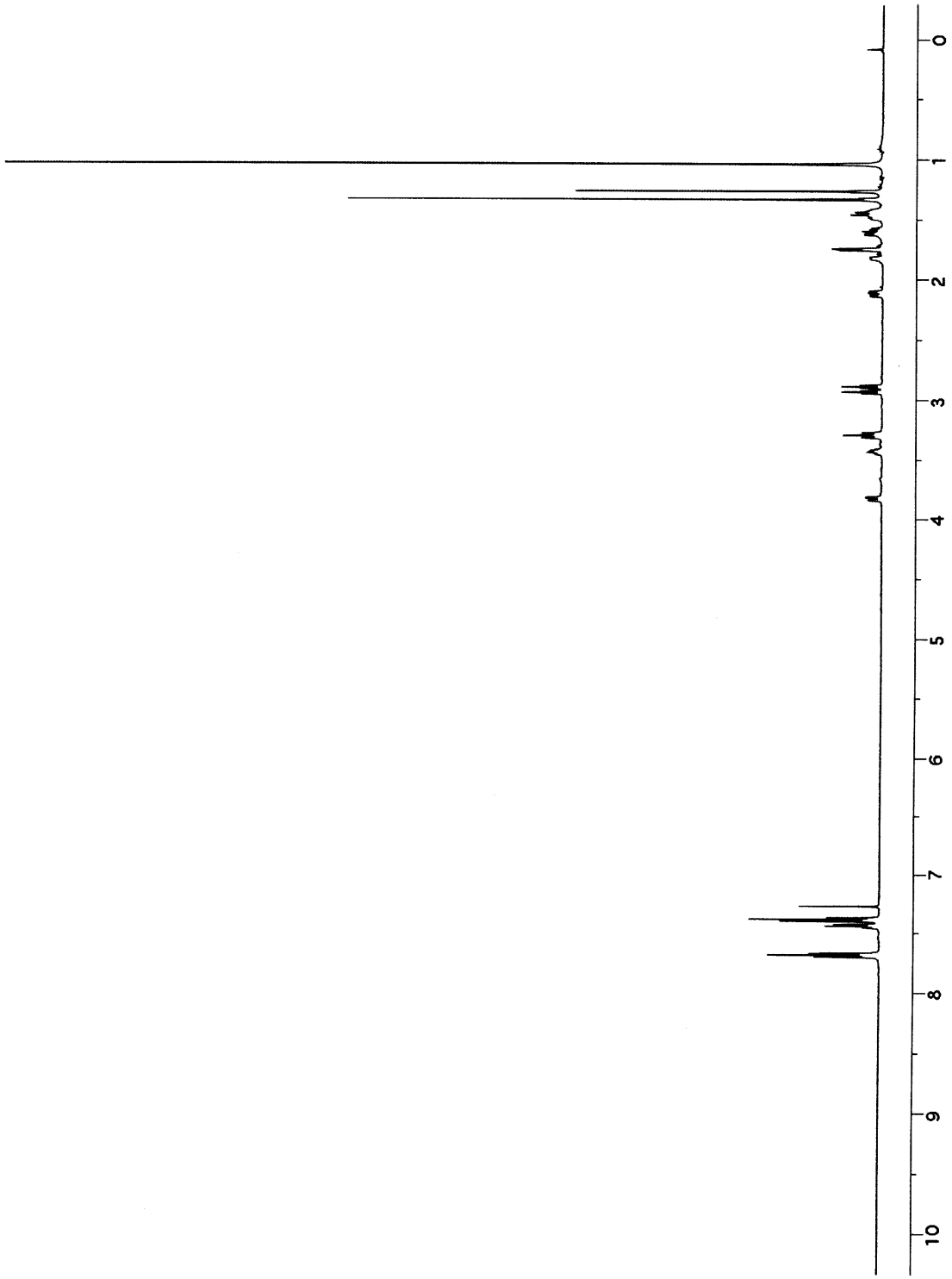

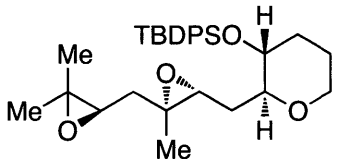

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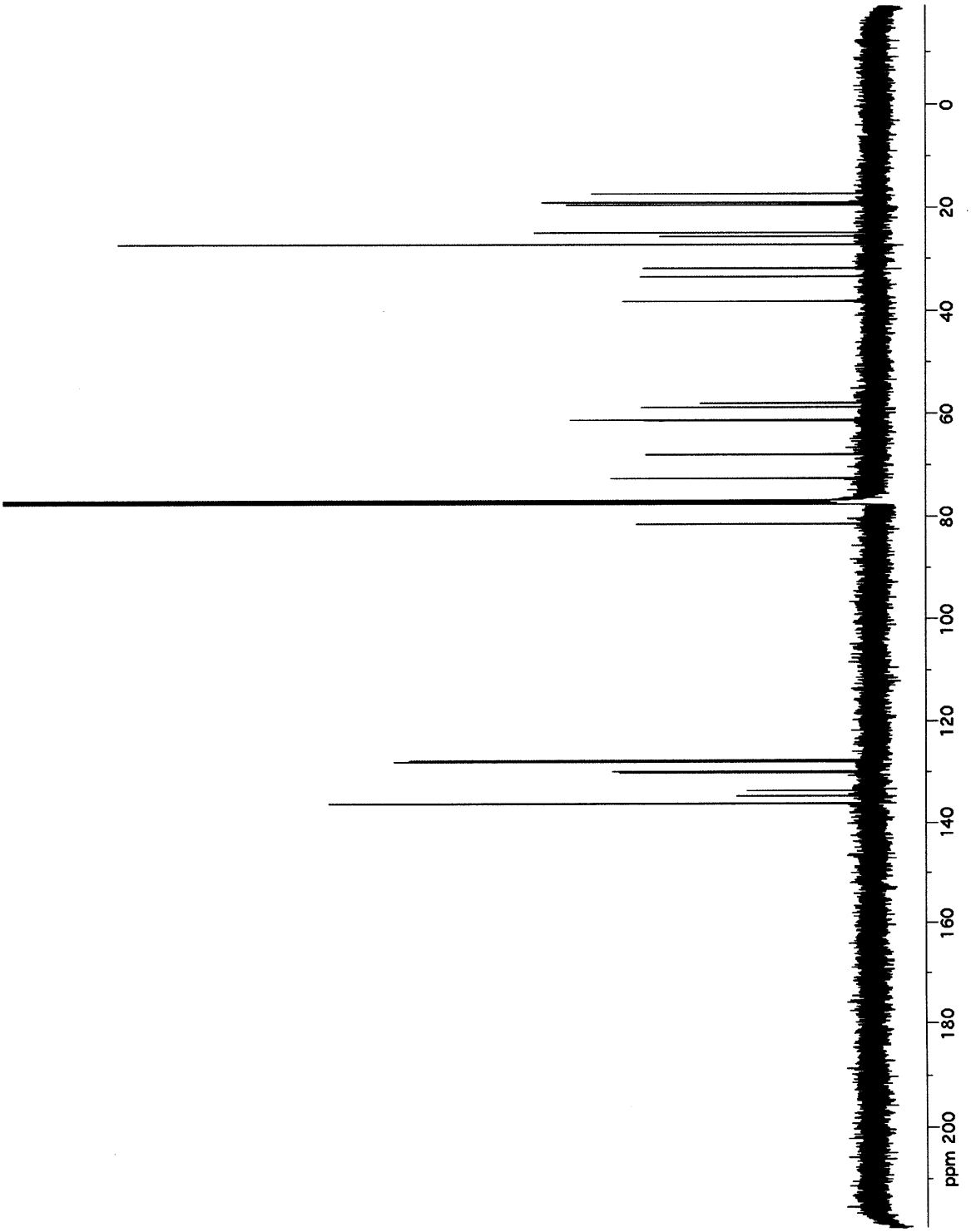

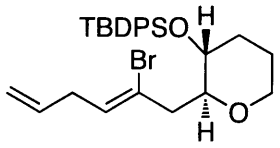

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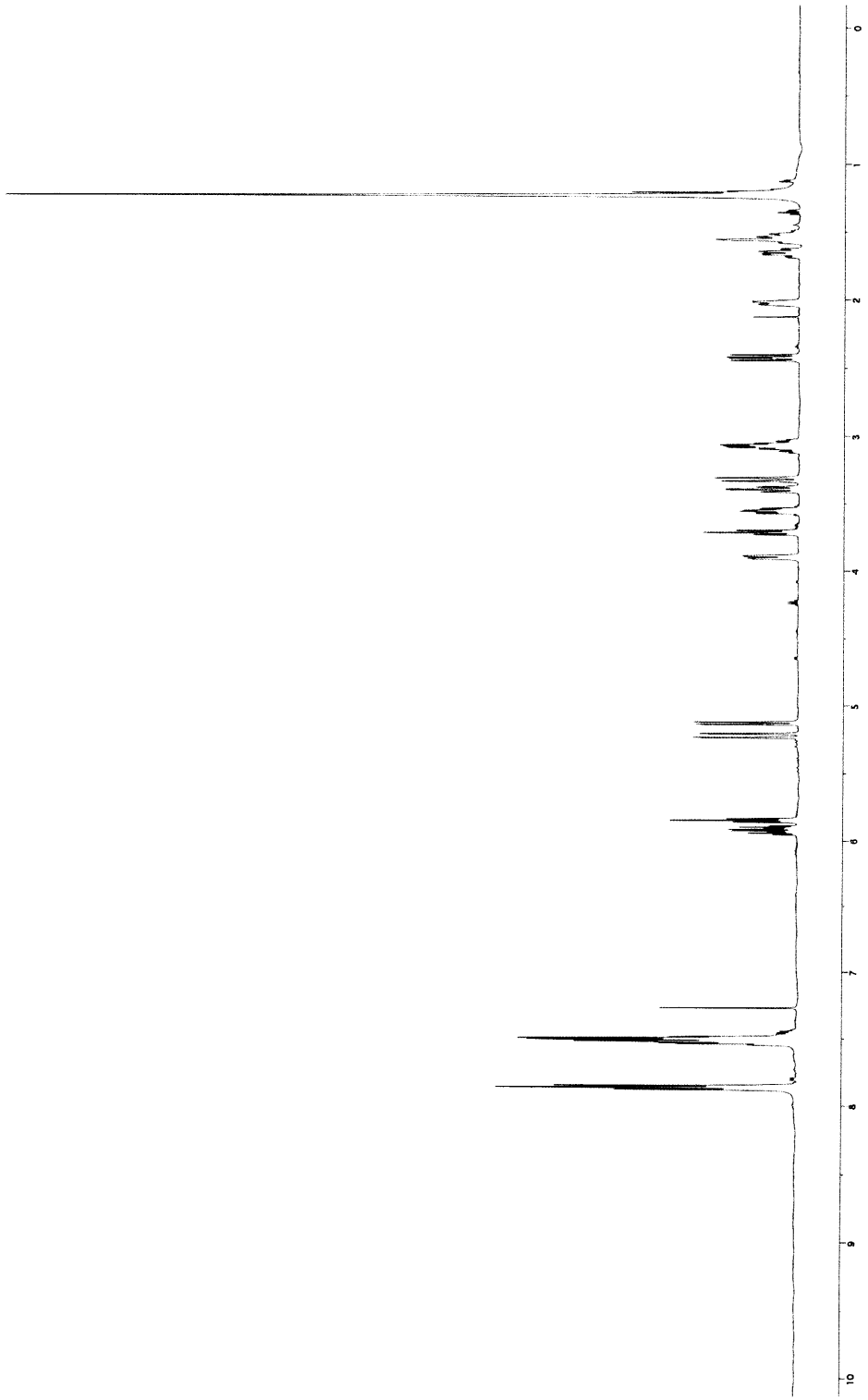

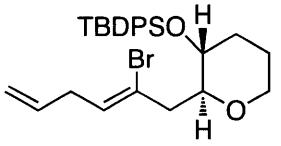

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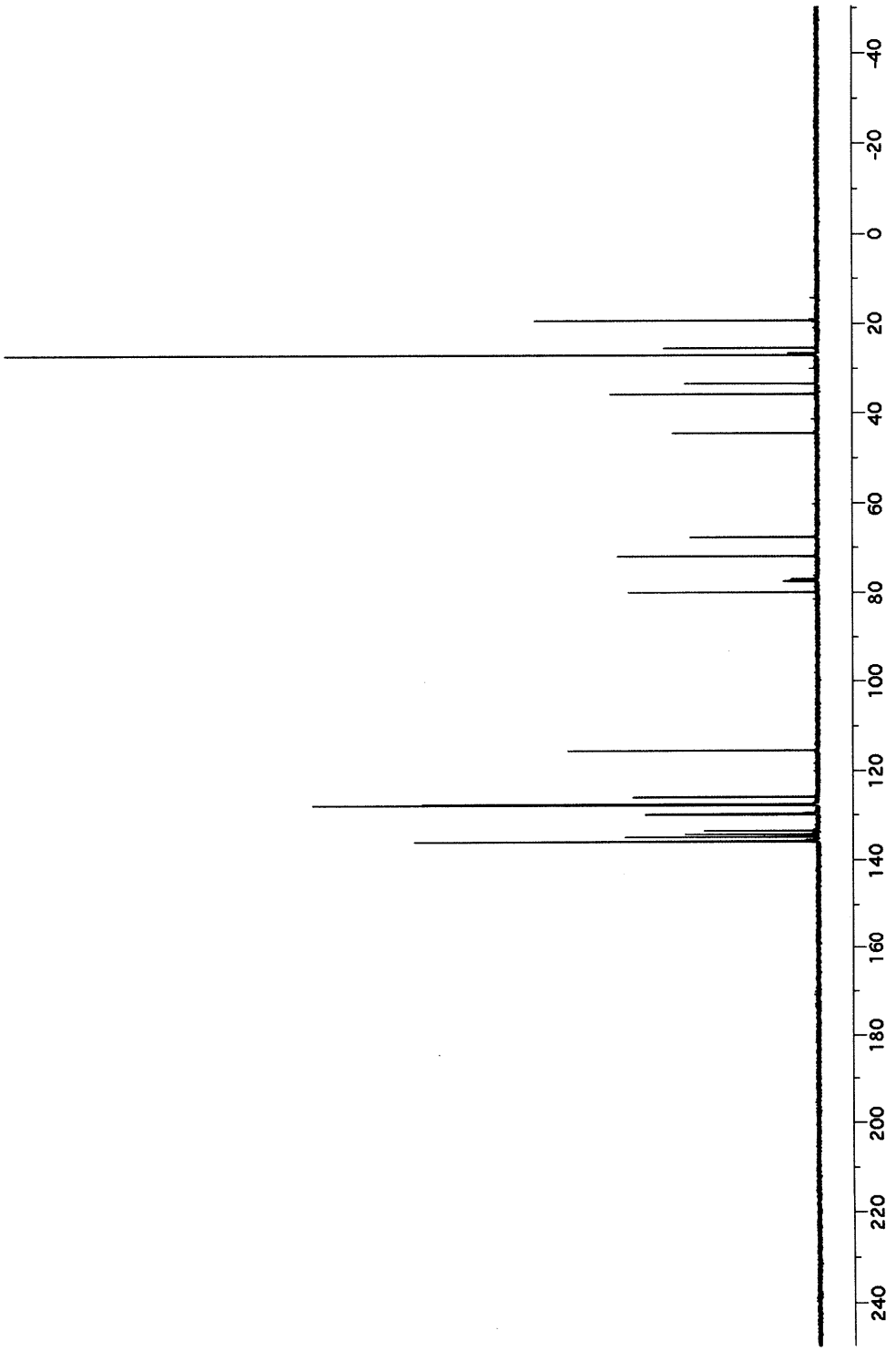

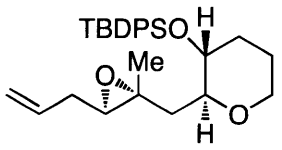

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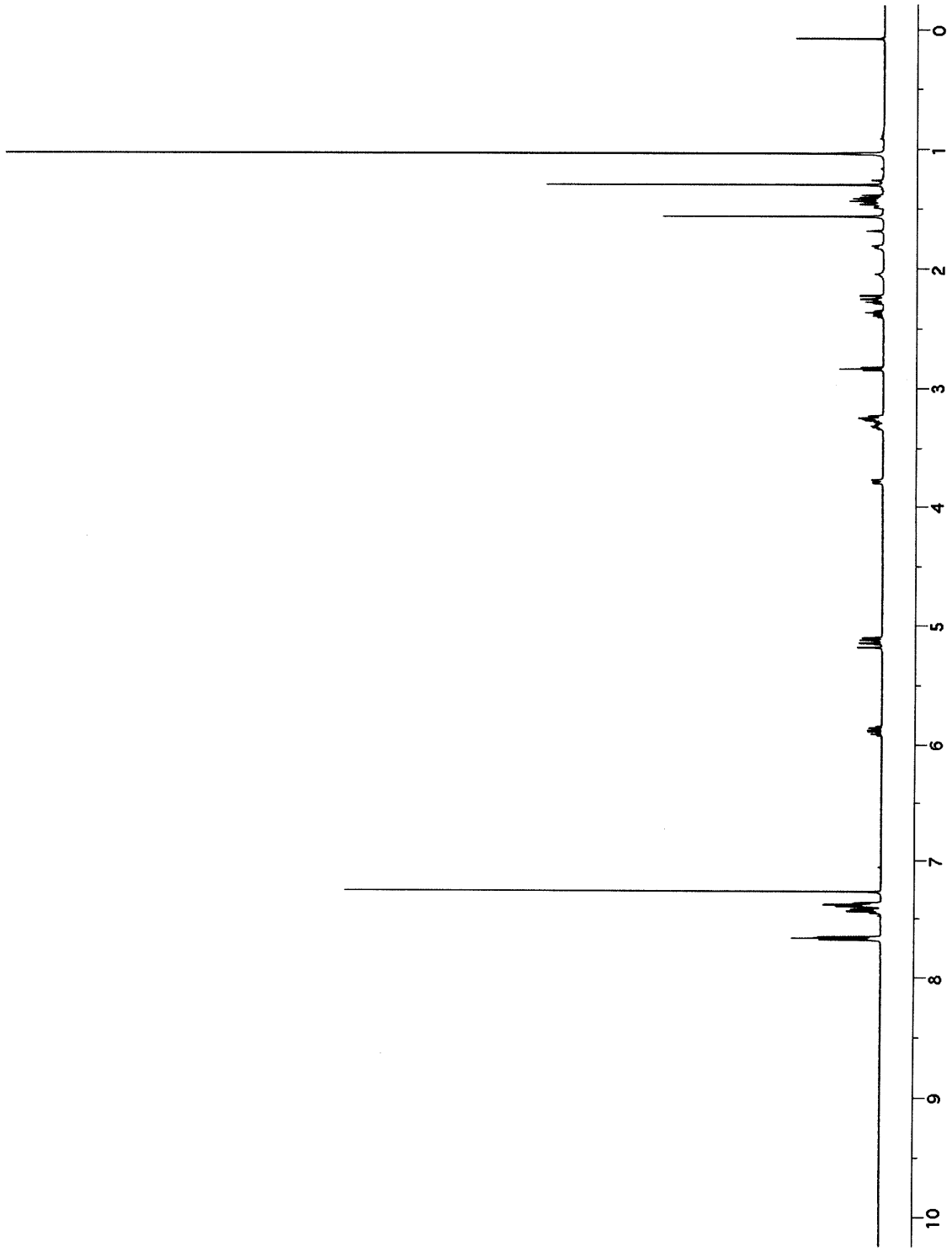

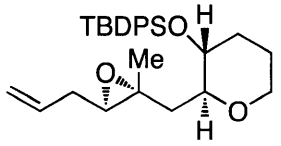

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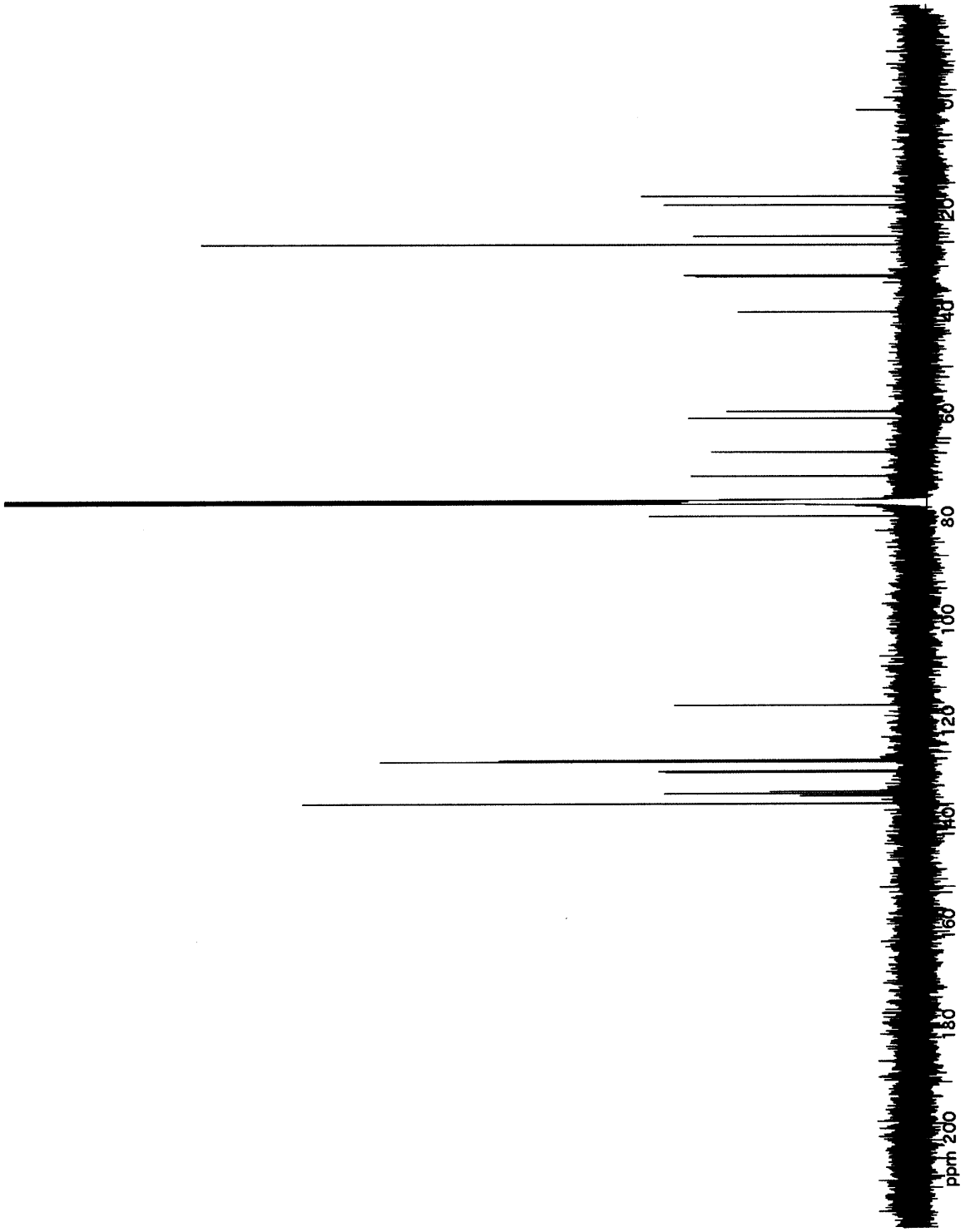

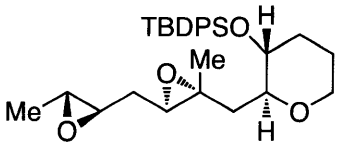

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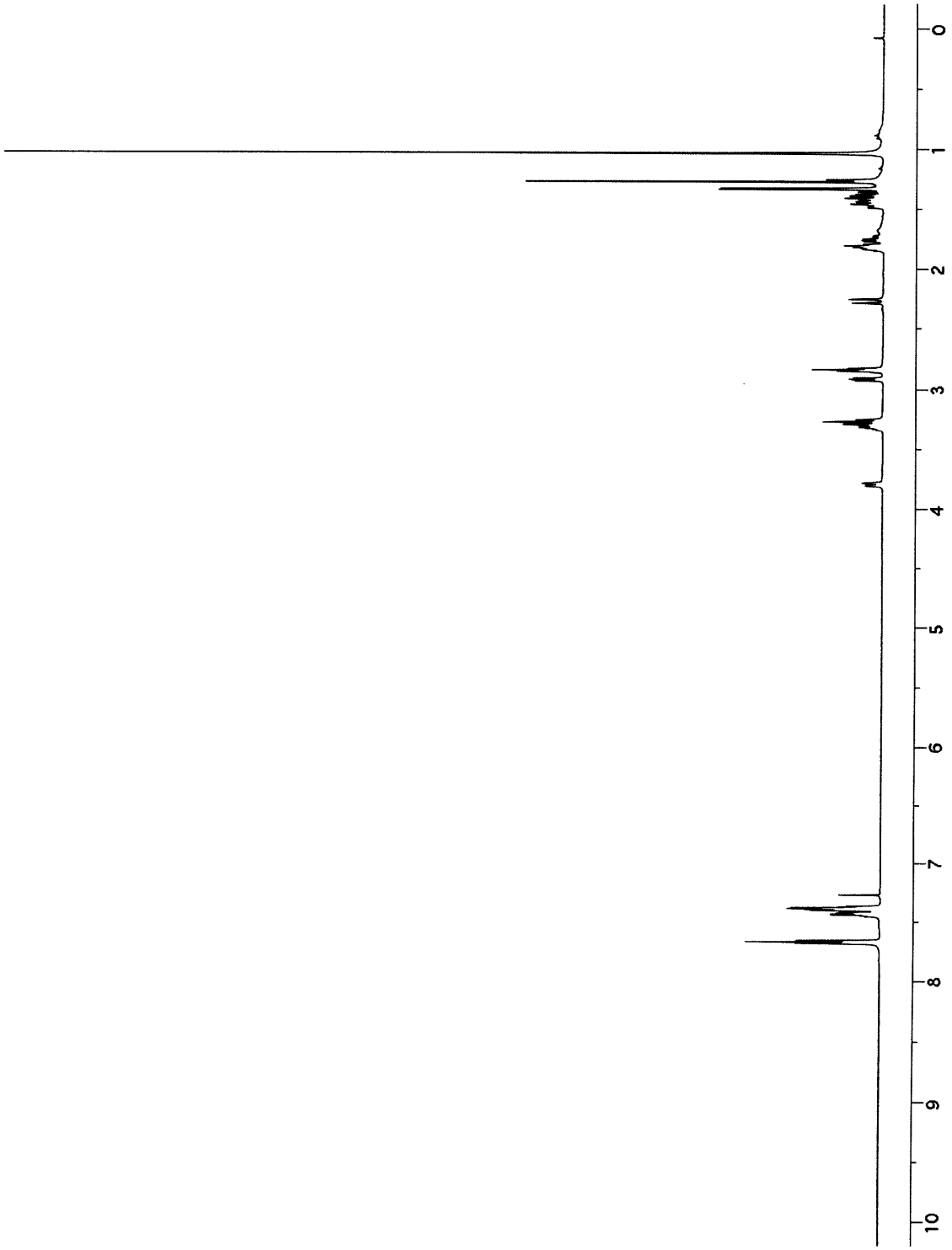

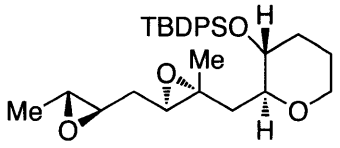

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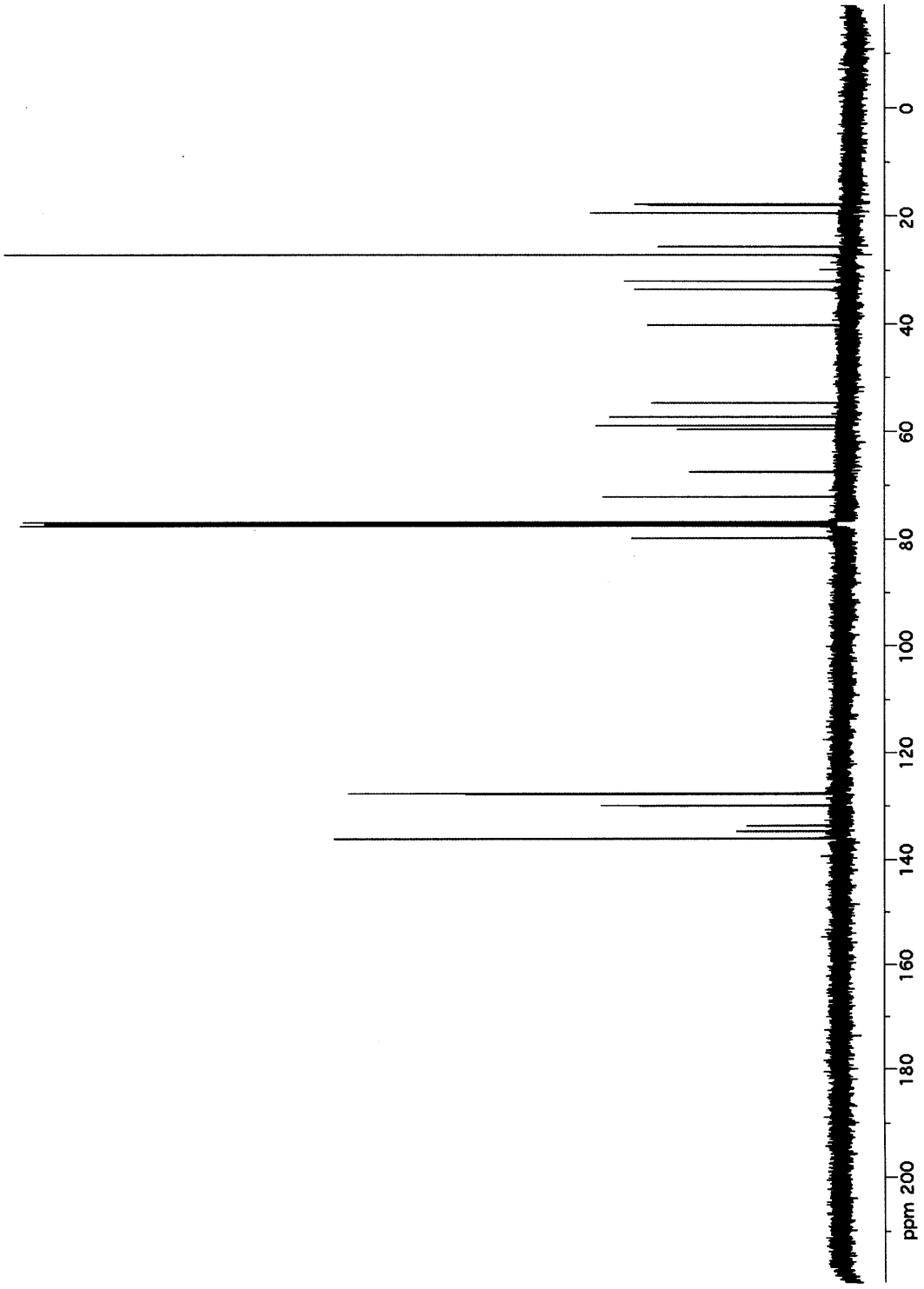

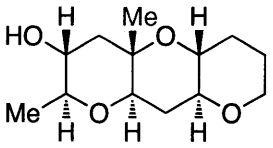

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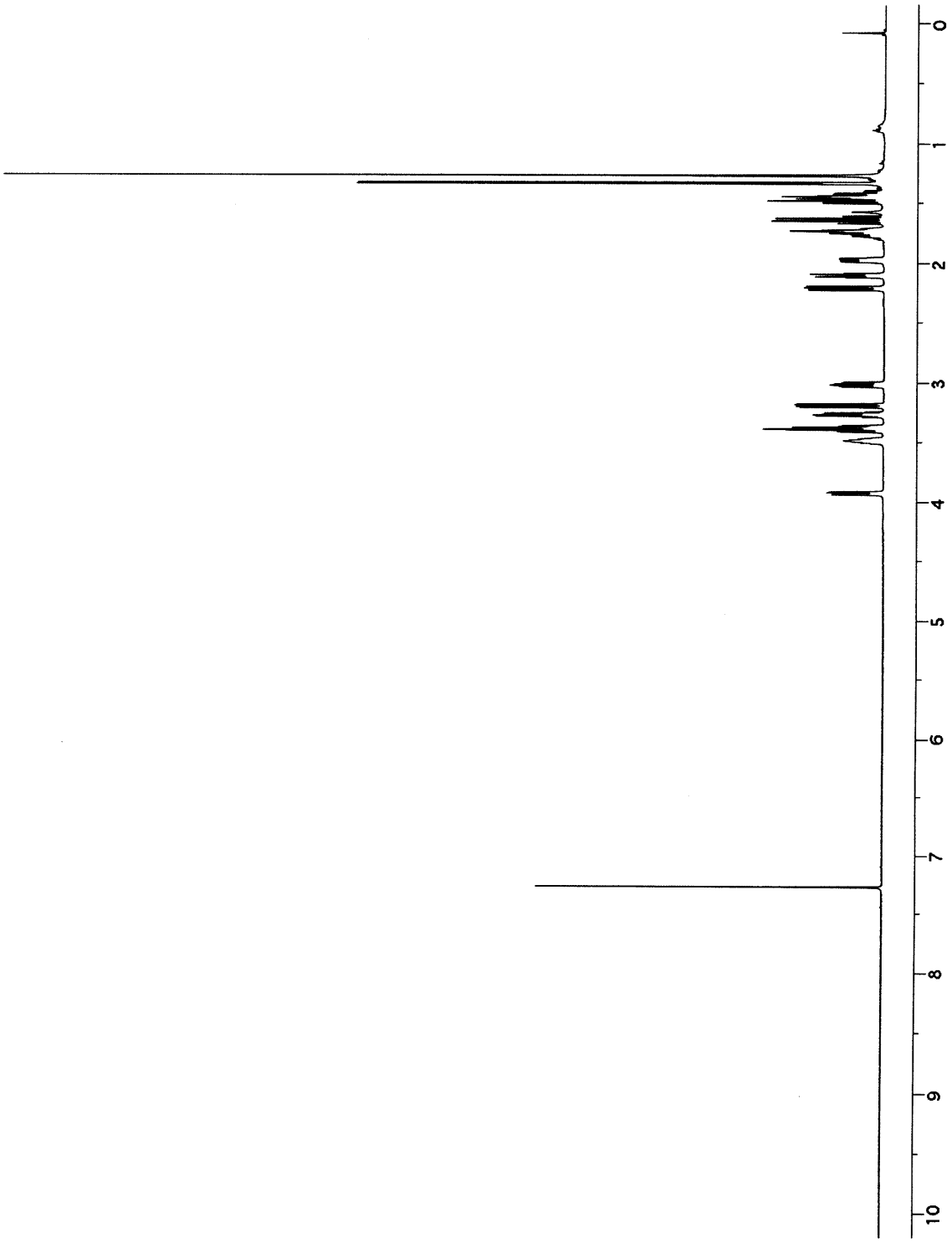

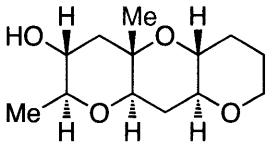

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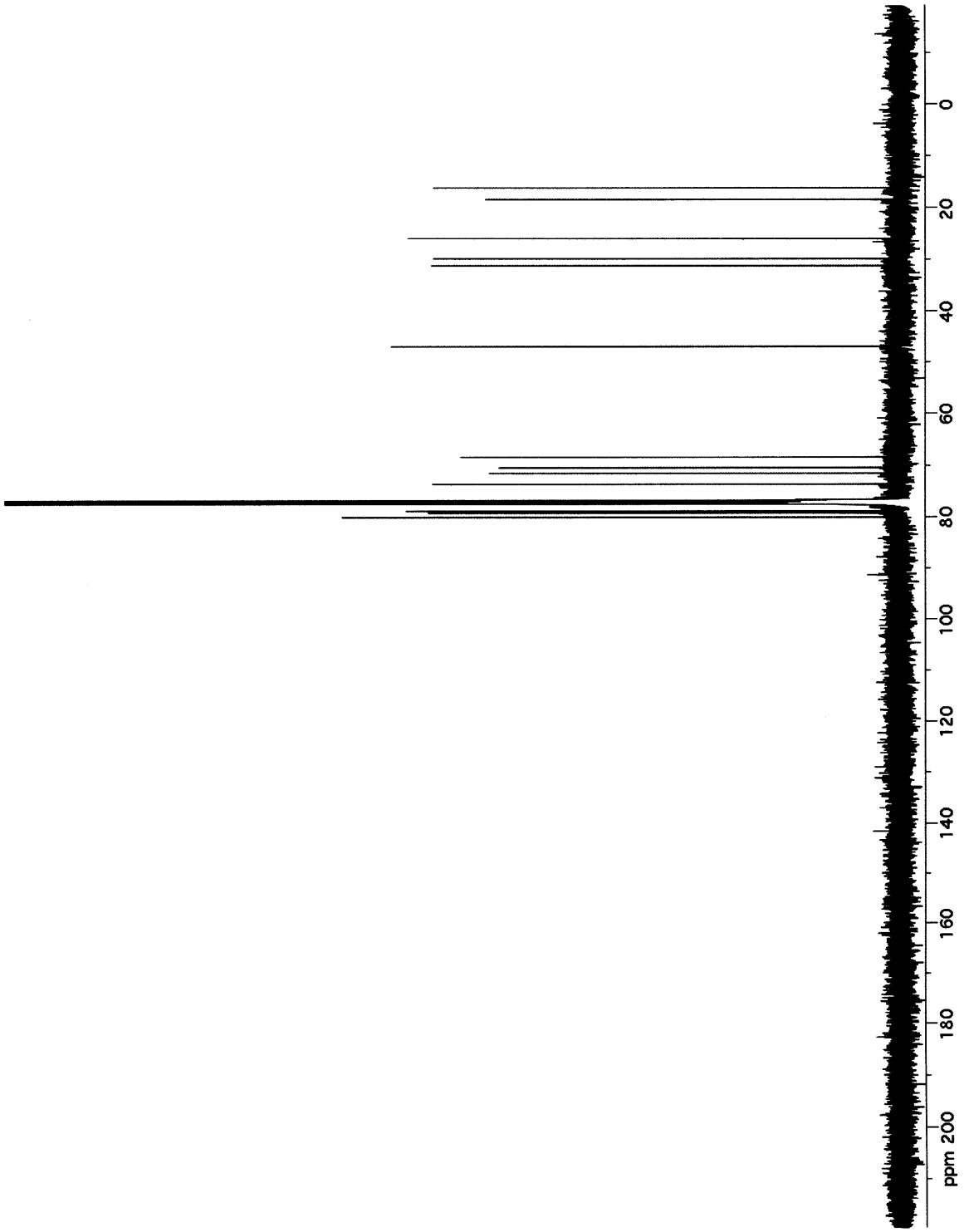

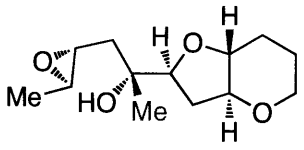

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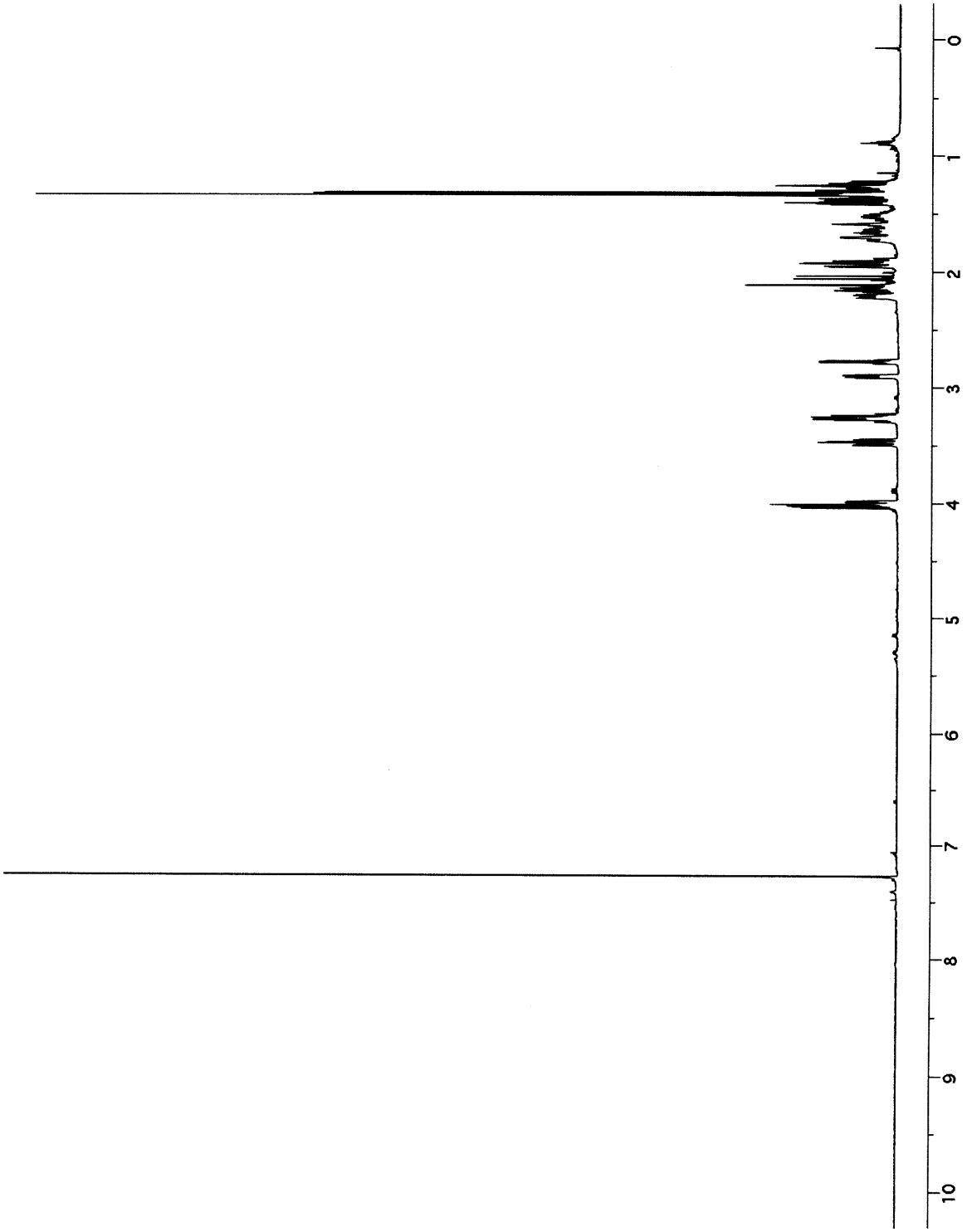

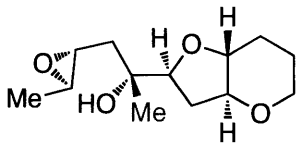

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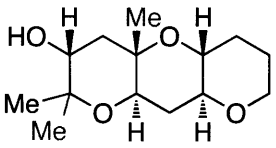

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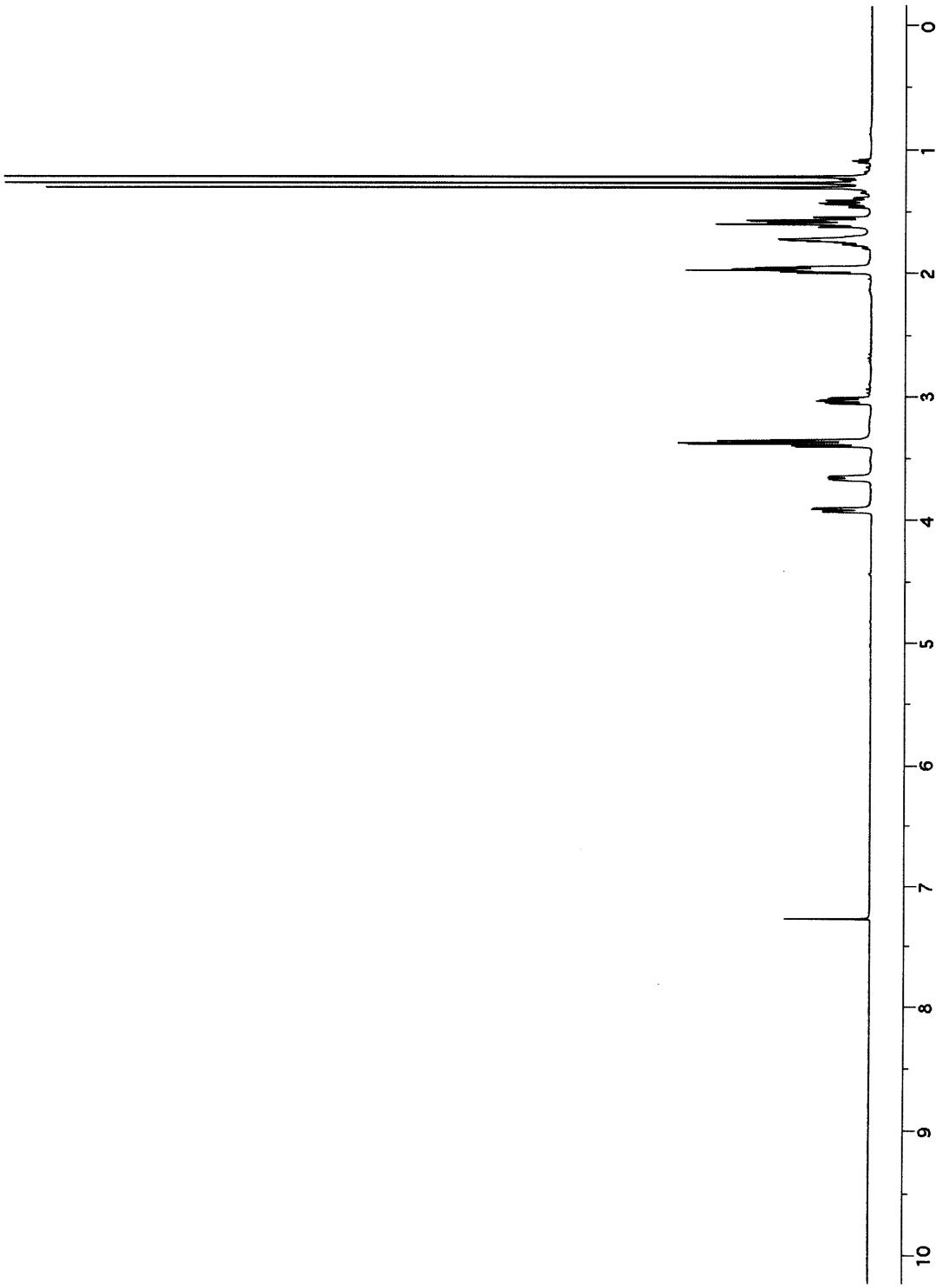

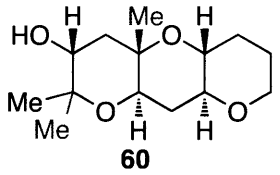

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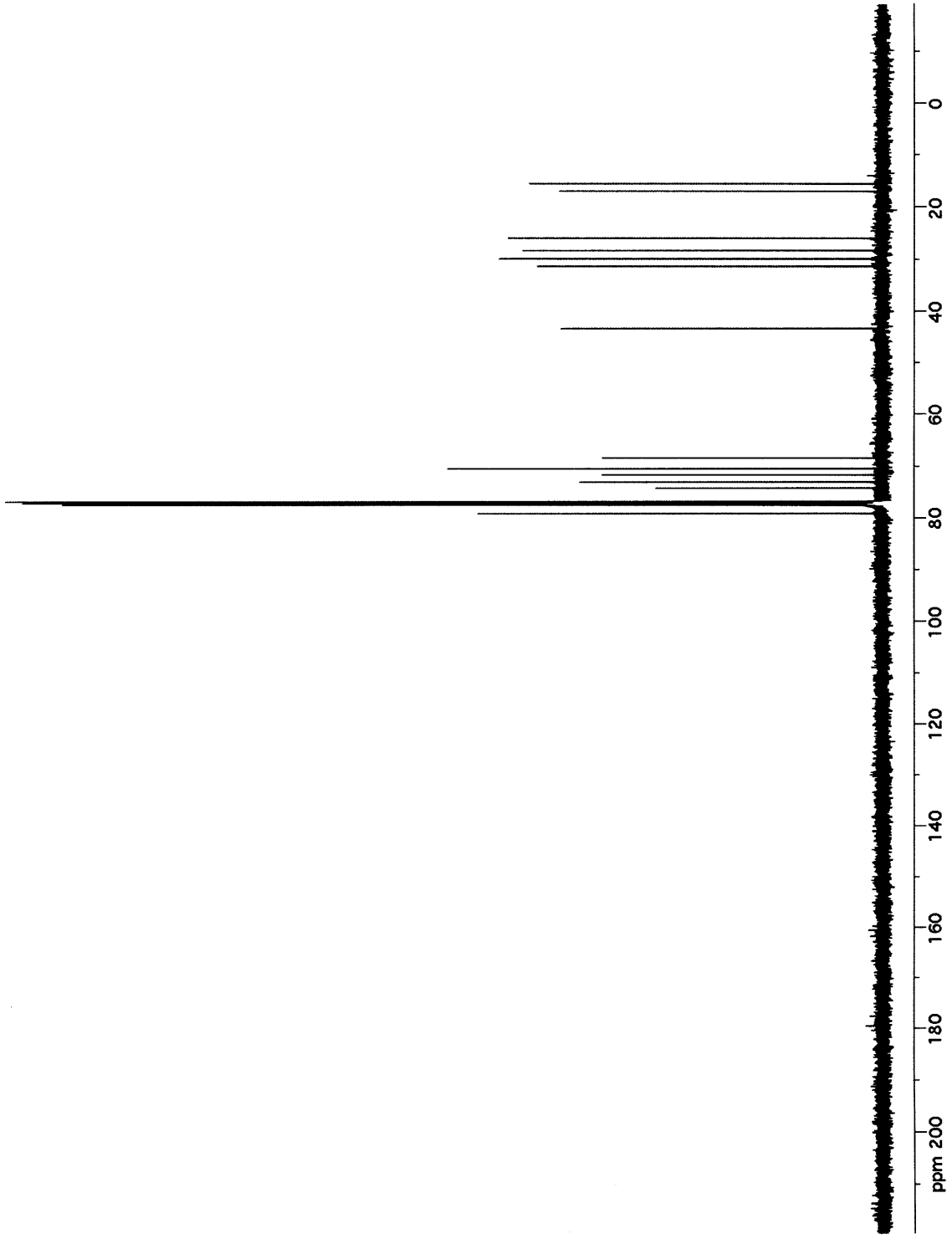

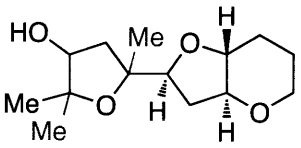

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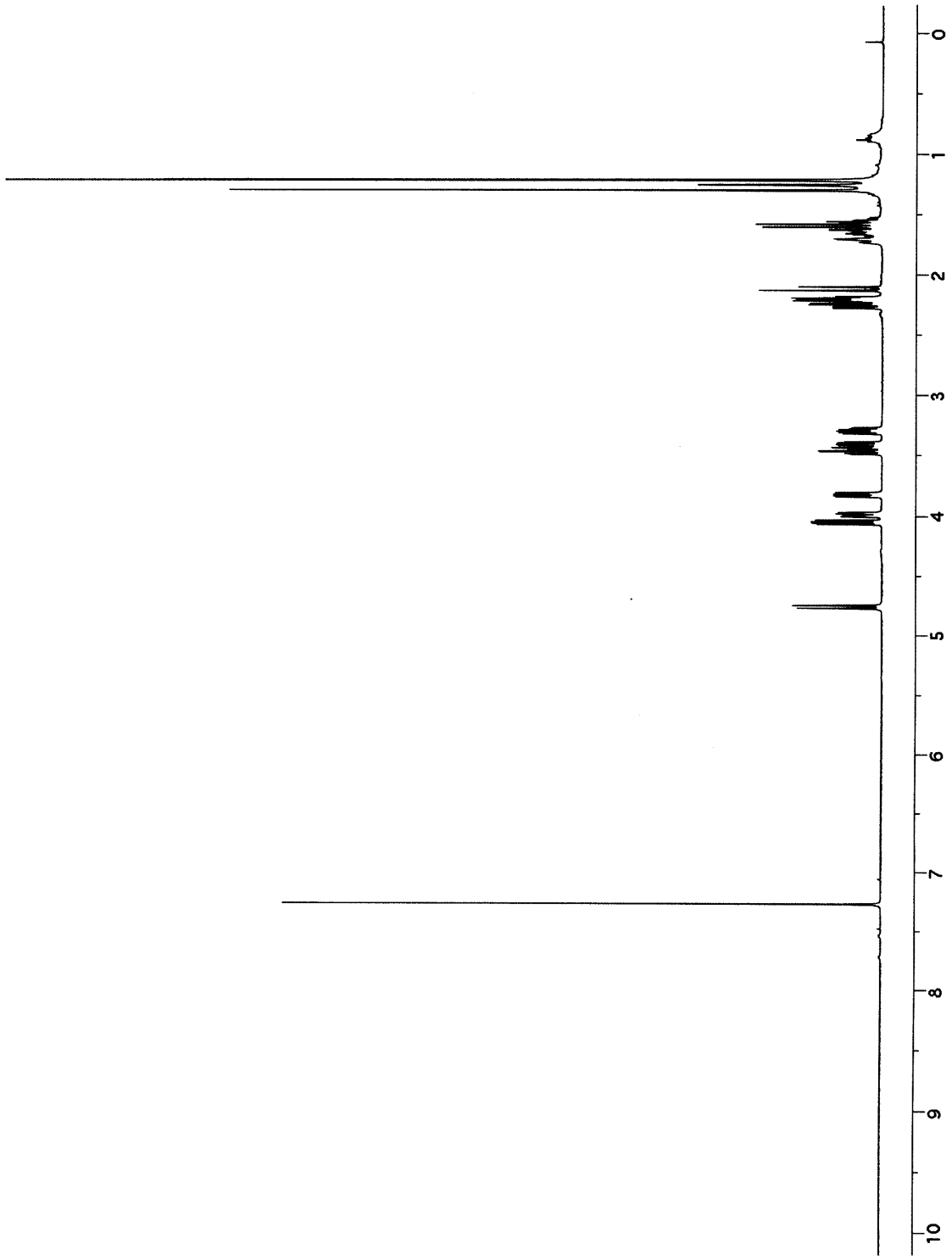

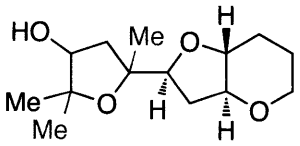
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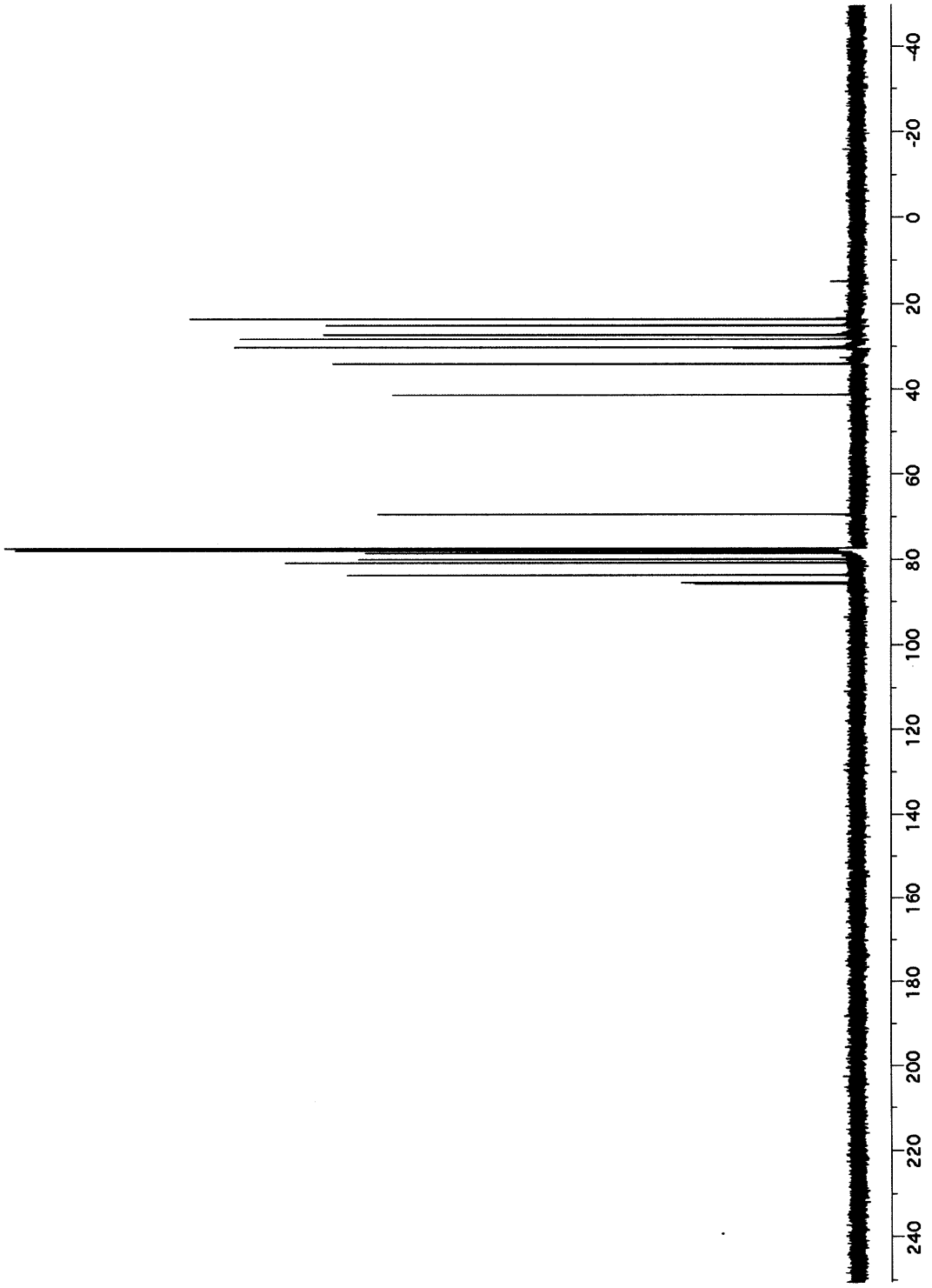
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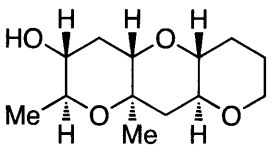

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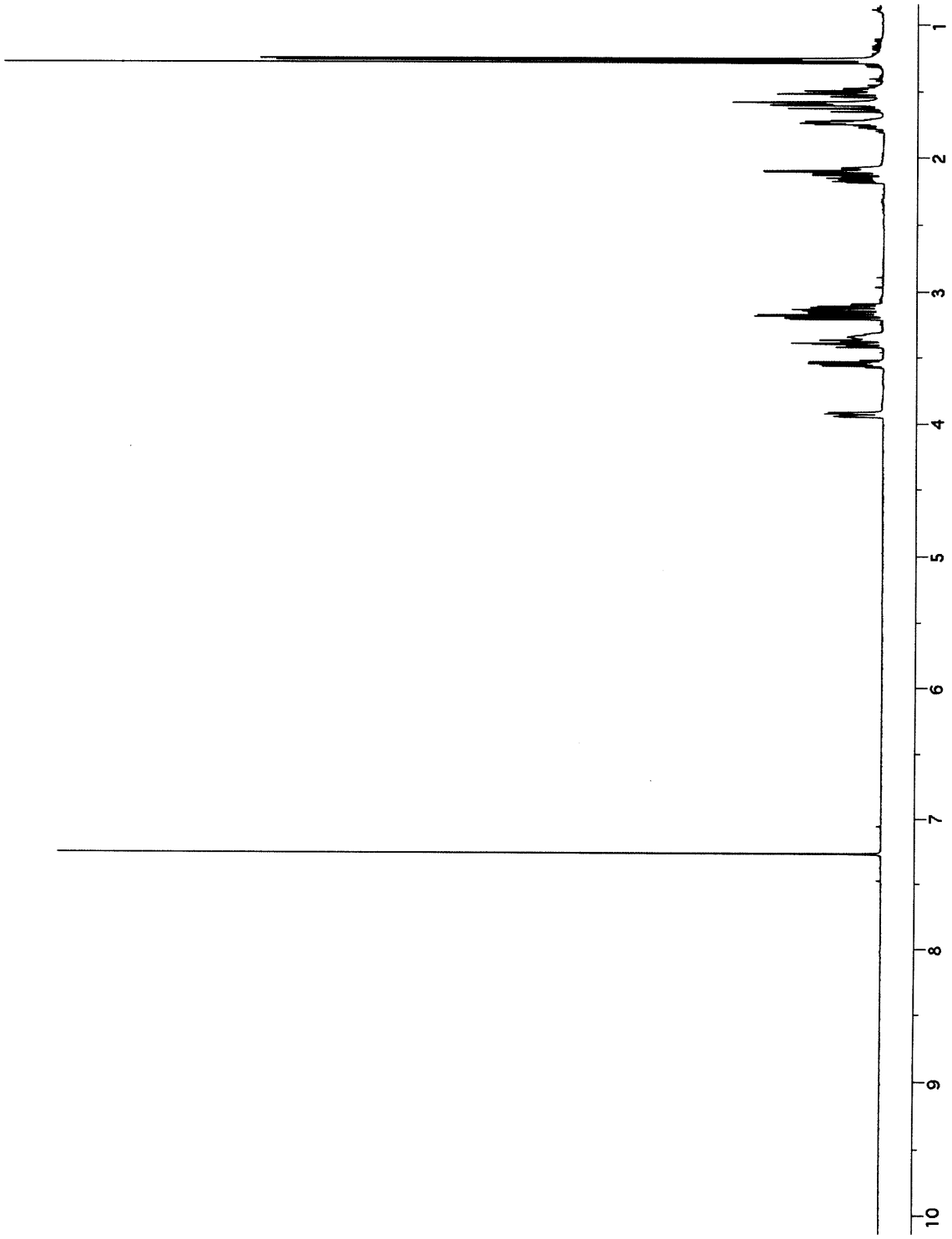

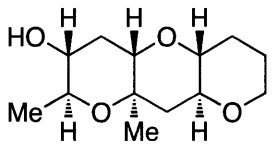
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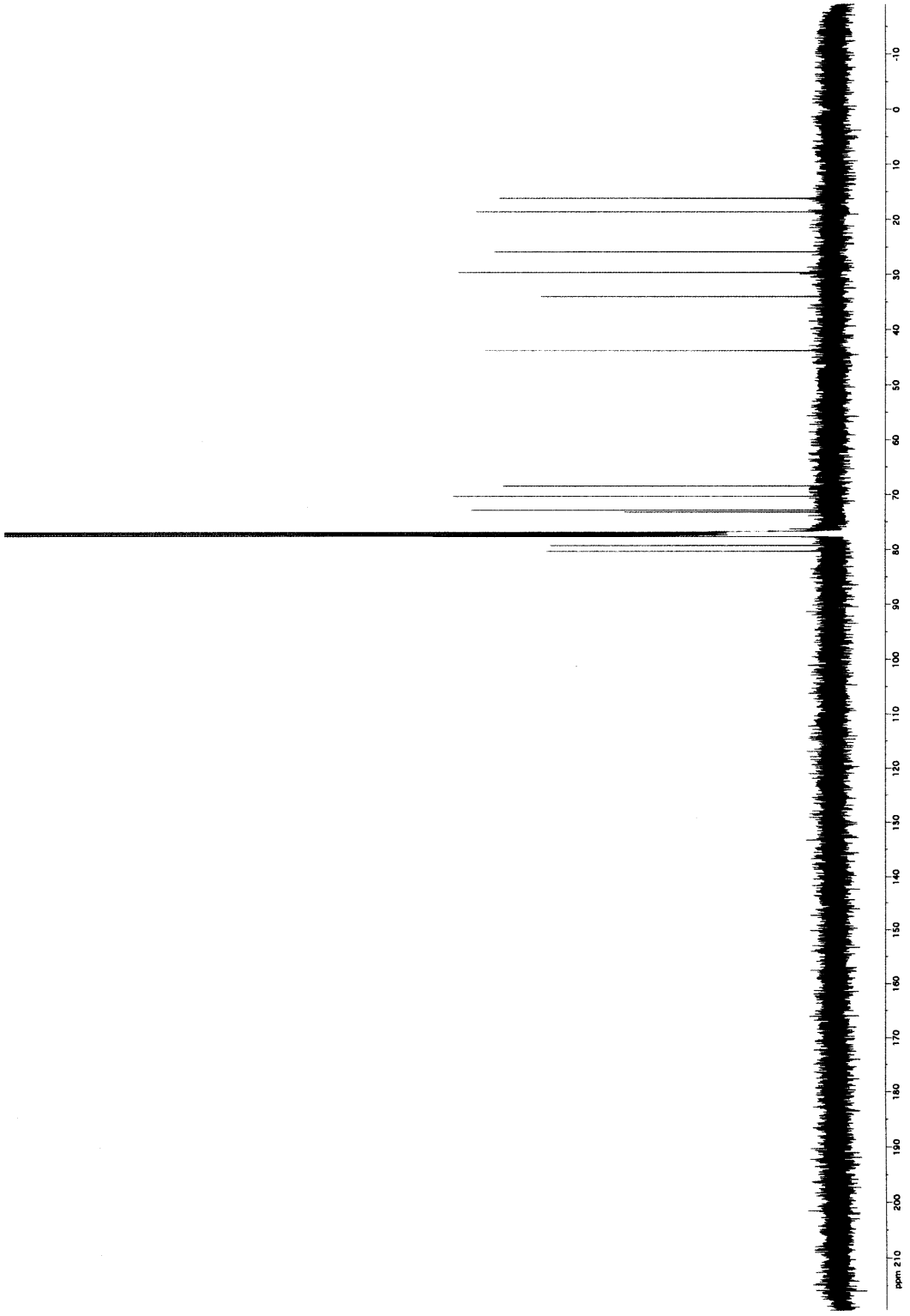
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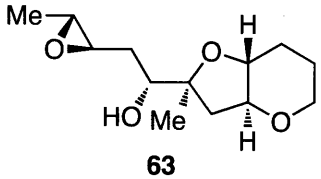

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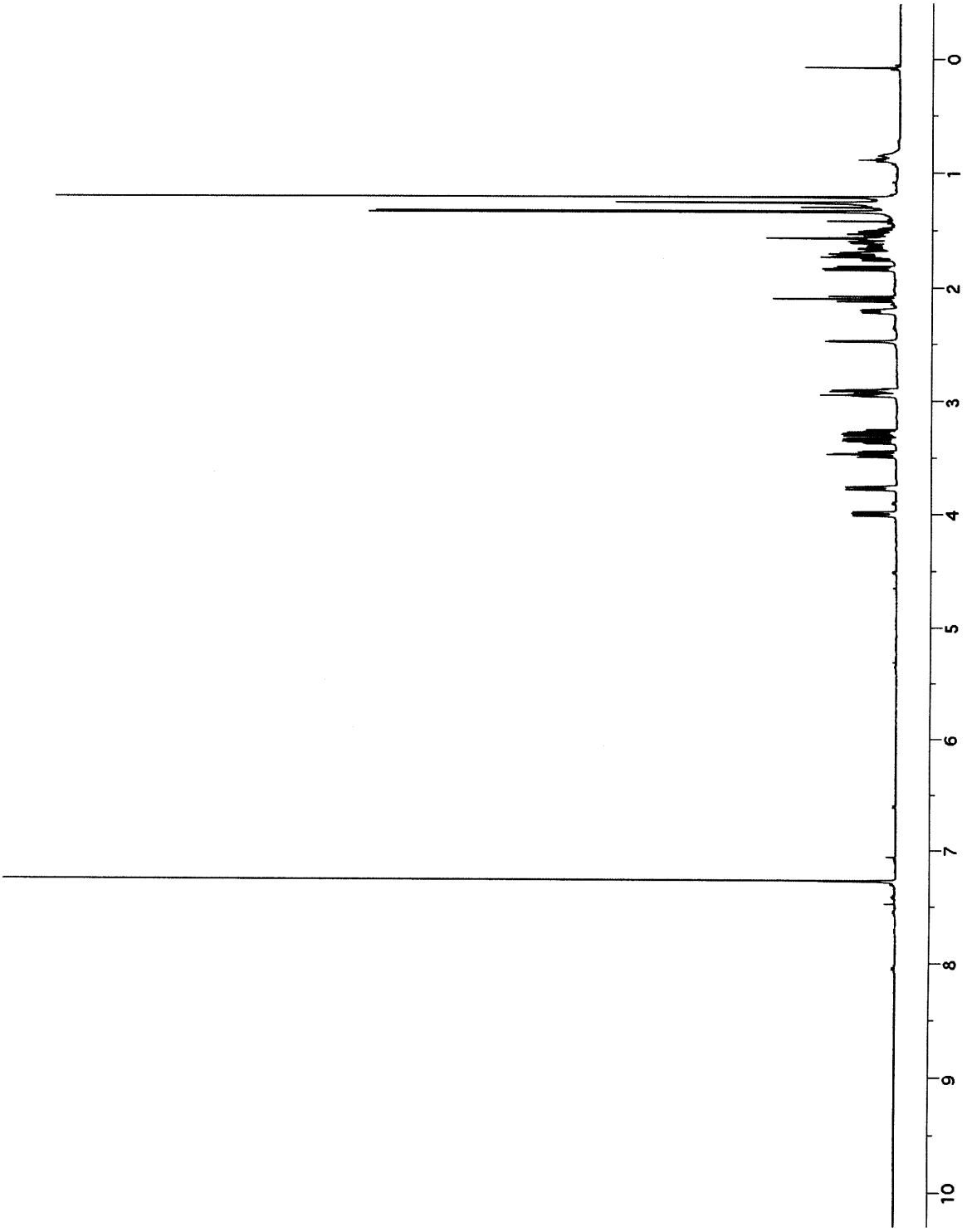

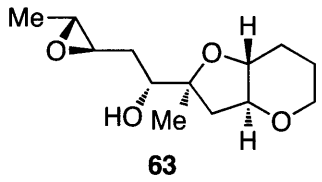

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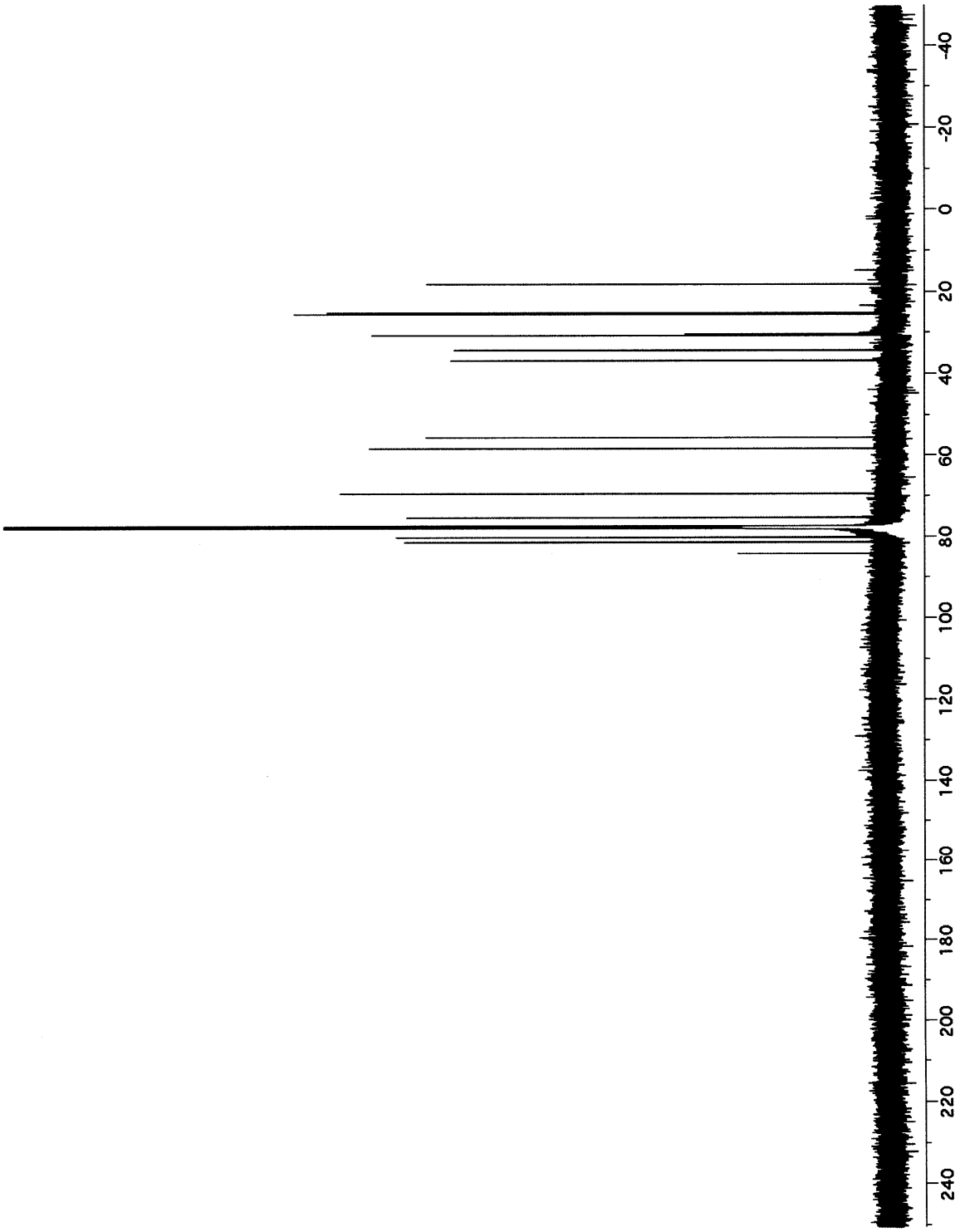

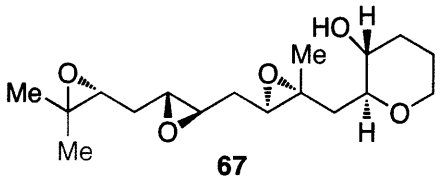

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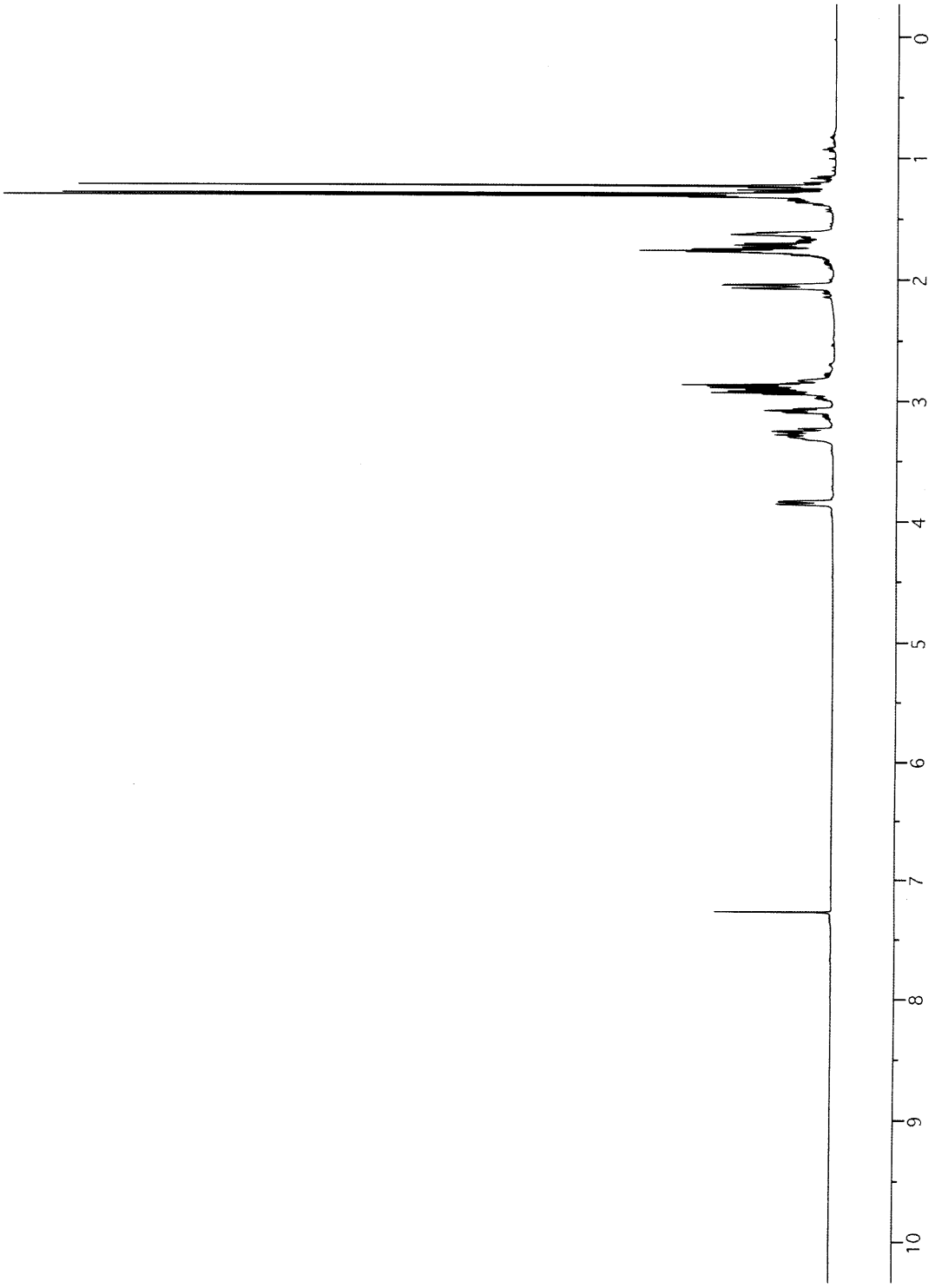

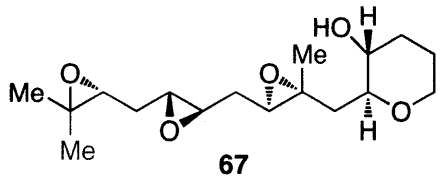

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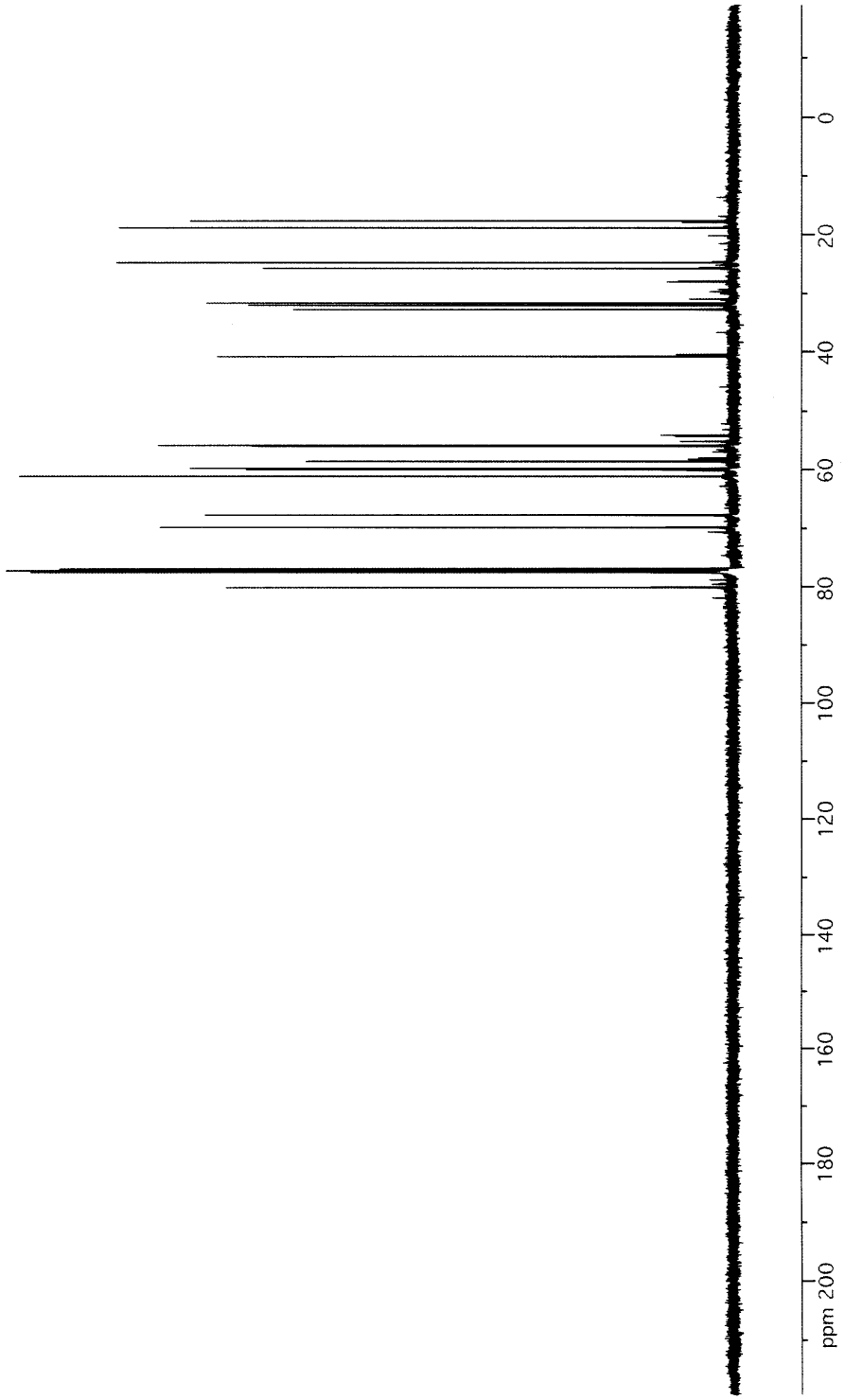

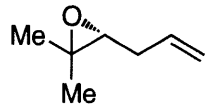

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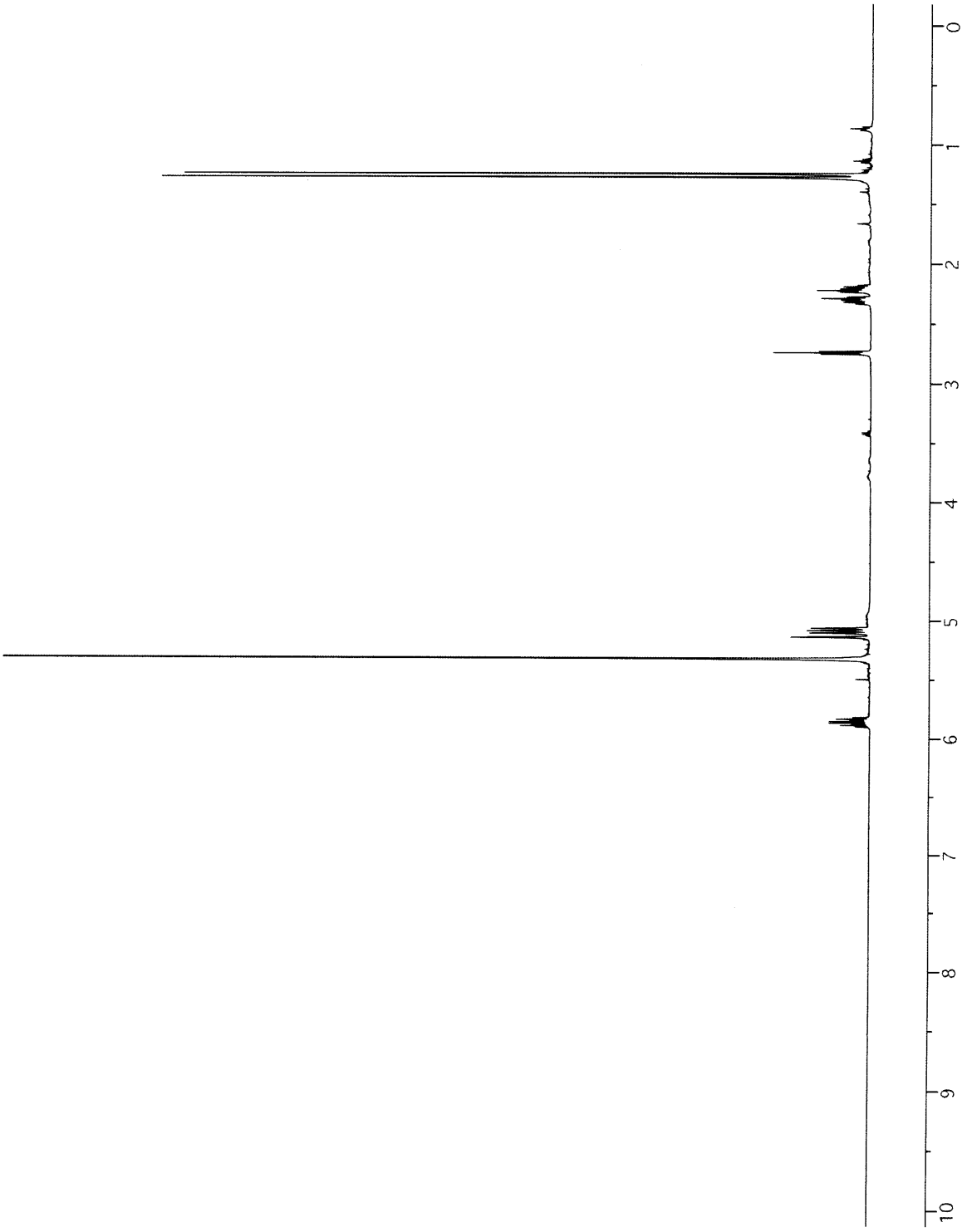
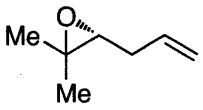
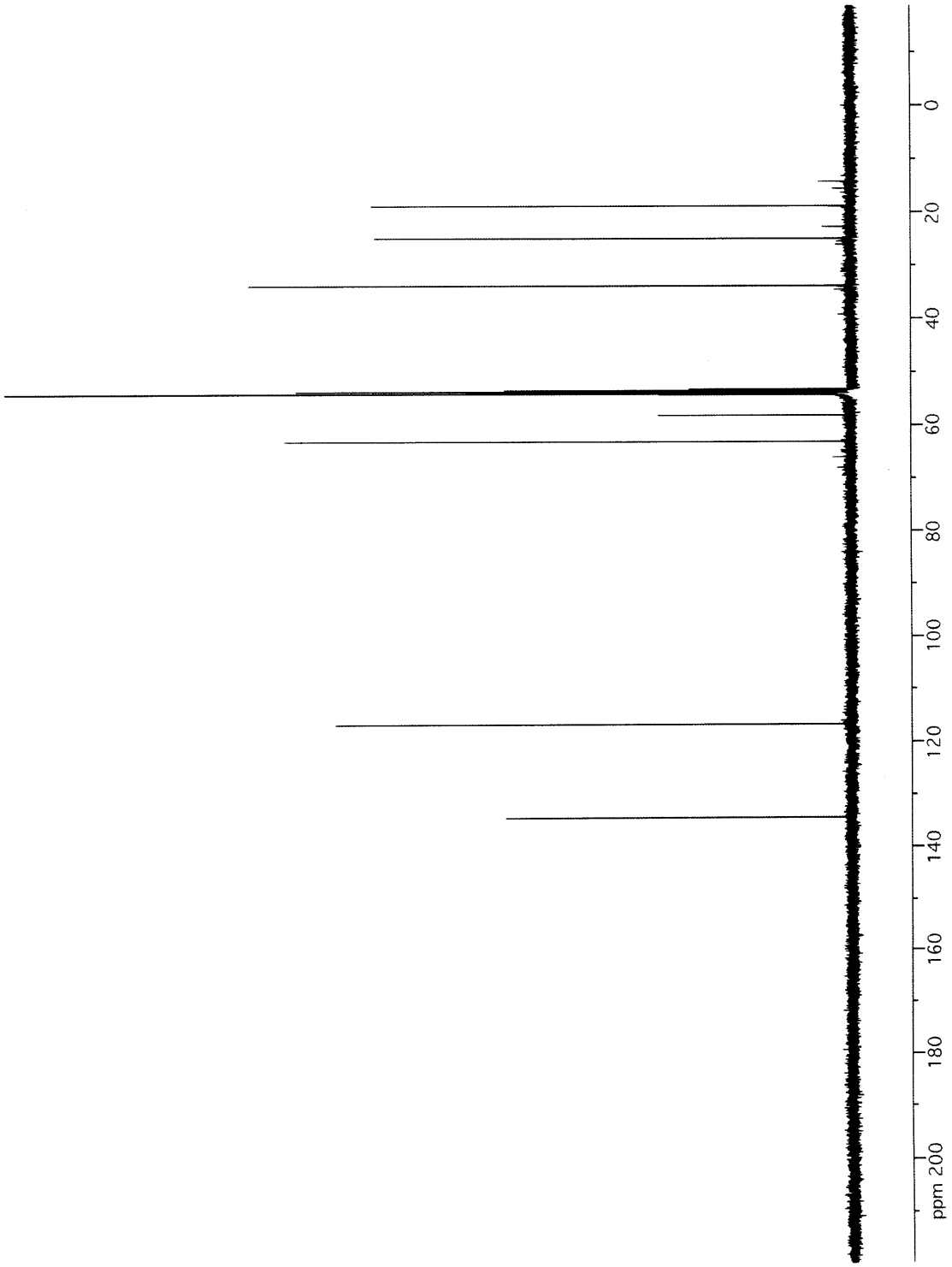
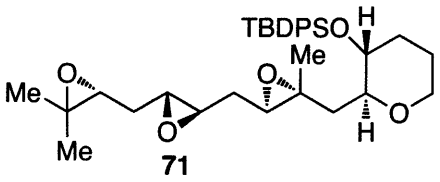




70





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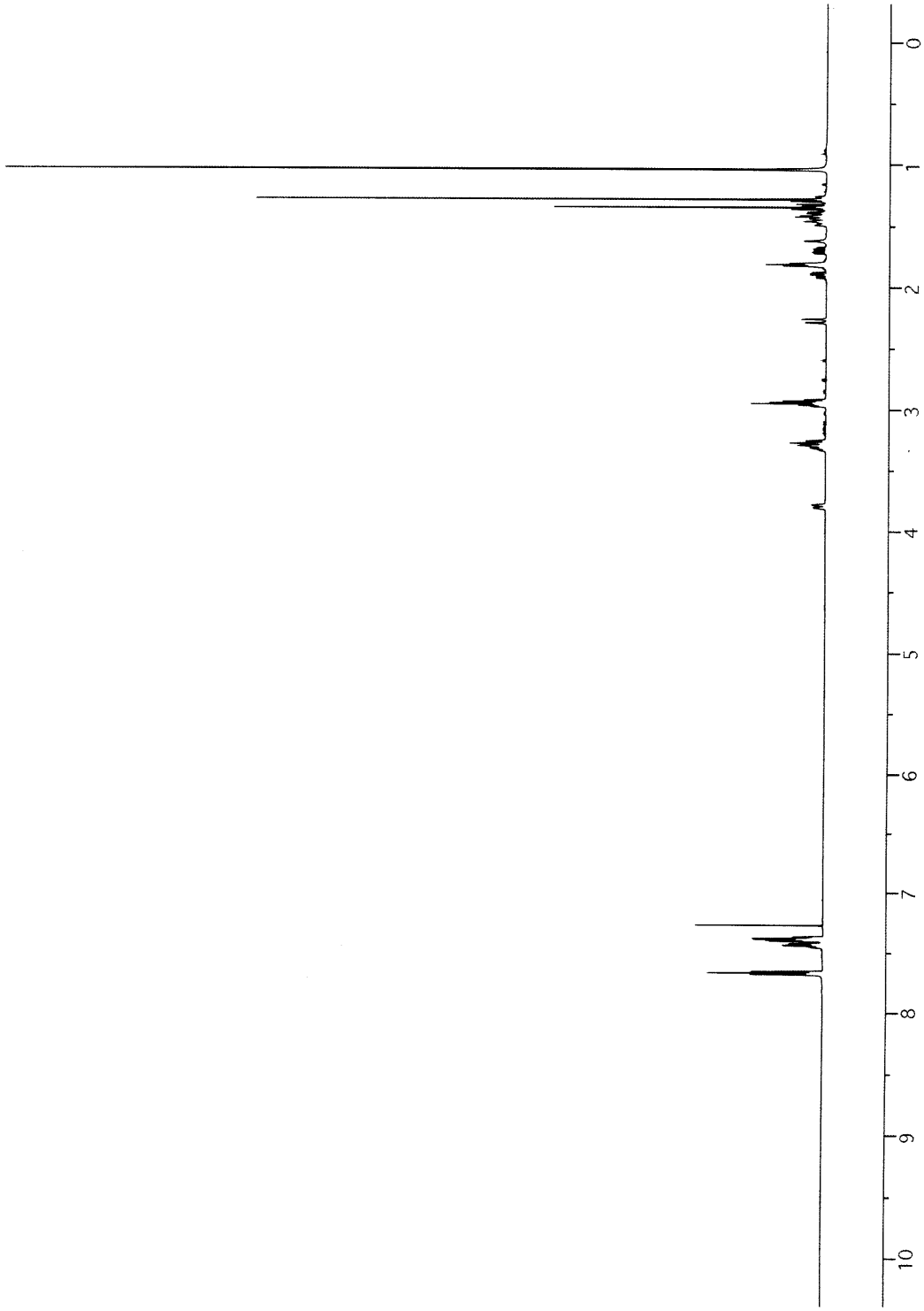

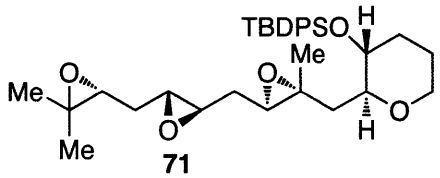

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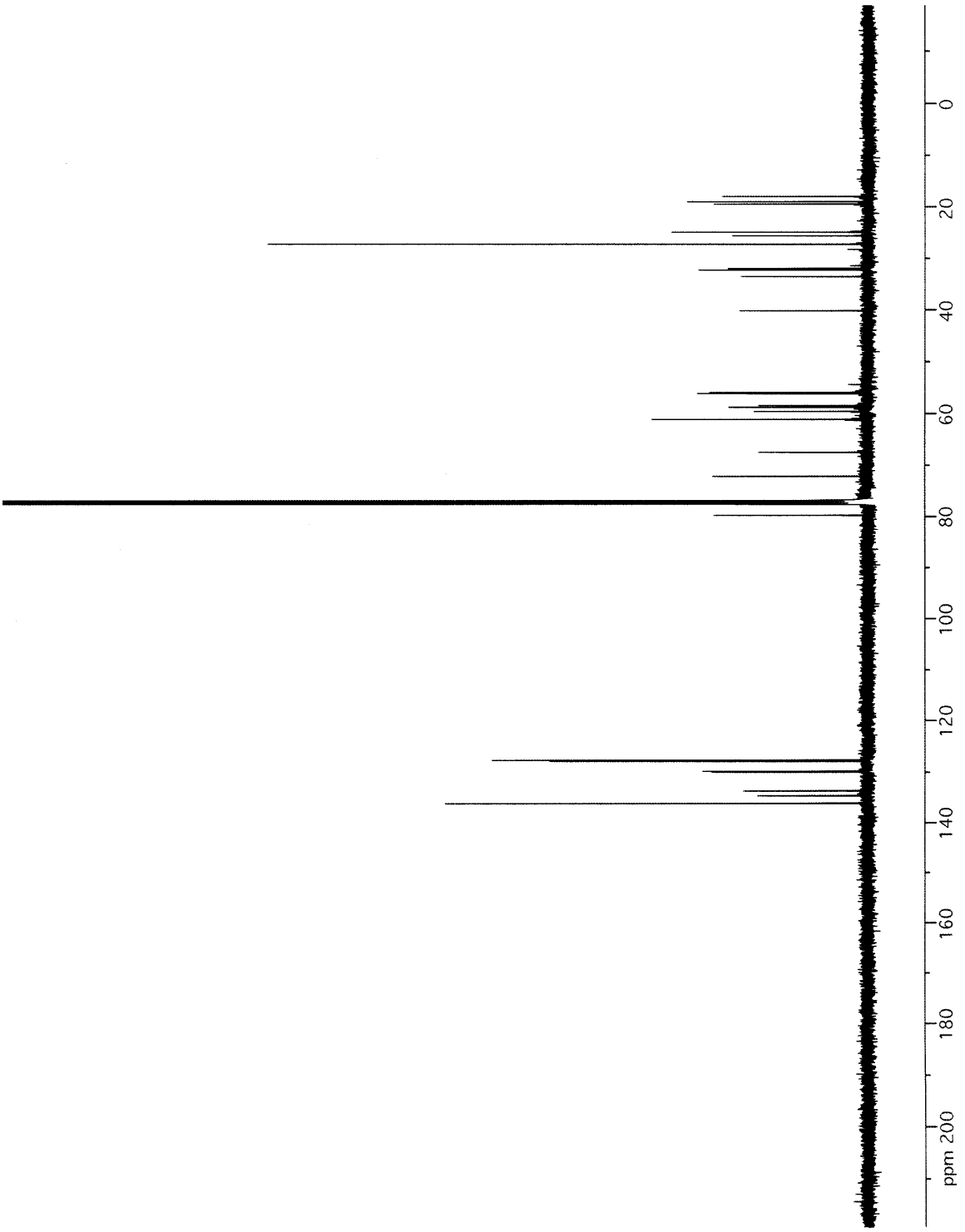


Chapter III

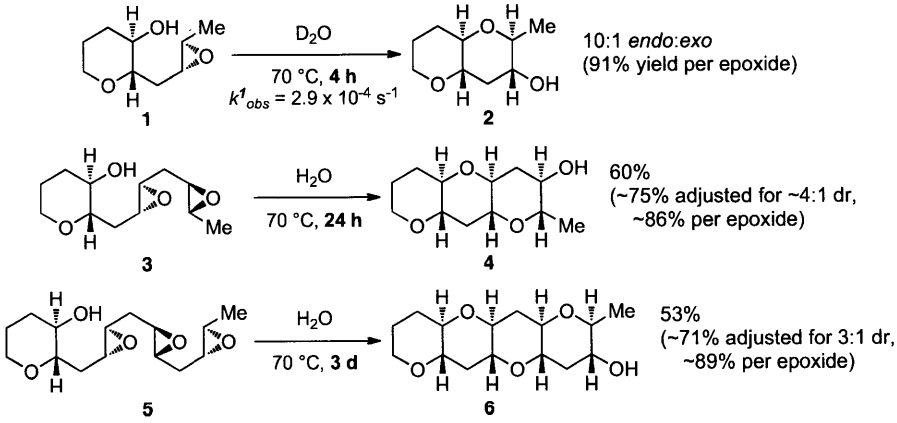
Kinetics of an Epoxide-Opening Cascade Promoted by Neutral Water. Evidence for a Stepwise Mechanism.[1]

[1] This project was carried out in collaboration with Dr. Jeffery A. Byers of the Jamison research group, MIT.

A. Introduction to the unresolved question of the mechanism of epoxide-opening cascades promoted by water.

In Chapter II, we studied a number of *endo*-selective epoxide-opening cascades promoted by water. Two important questions were raised. First, why are cascade reactions so much slower than cyclizations of a single epoxide (Scheme 1)? That is, why do the cascade reactions of diepoxy alcohol **3** and triepoxy alcohol **5** require heating not two or three but six or 18 times times longer than monoepoxy alcohol **1**?[2] Second, why are yields in certain cascade reactions so much lower than one would expect, given the high regioselectivities observed in discrete cyclizations of their component epoxides? (See, for example, Scheme 16 in Chapter II.)

Scheme 1. Significant differences in reaction rate in epoxide-opening cascades promoted by water. (Vilotijevic and Jamison, ref. 2a, and Byers and Jamison, ref. 2b)



We had initially, and perhaps somewhat naively, assumed a stepwise mechanism for *endo*-selective epoxide opening promoted by water. However, there is extensive precedent for concerted mechanisms in cascades of cyclization reactions. Perhaps most famously, lanosterol and descendent steroids are derived in large part from concerted

[2] (a) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189. (b) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383. (c) Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, *38*, 3175.

polyene cascades.[3] There is also ample precedent for concerted cascades of *endo* epoxide opening, from the work of McDonald,[4] Floreancig,[5] and our own group.[6] Even in the epoxide-opening cascades originally proposed for the biosynthesis of the brevetoxins, as laid out by Nakanishi[7] and Shimizu,[8] the question of whether cyclization is stepwise or concerted was left ambiguous.

We elected to study an epoxide-opening cascade reaction in water in detail. We chose a simple cascade of two epoxide openings, that of diepoxy alcohol **3**, which was first studied by Dr. Ivan Vilotijevic of the Jamison group. We chose this system because it was (and still remains) the highest-yielding cascade substrate identified by the group. The synthesis of **3** is described in Chapter II.

Close investigation of product mixtures from the reaction of diepoxide **3** in water revealed that the major side product was epoxy alcohol **7**, the result of *exo* cyclization of **3** (Scheme 2).[9] Indeed, careful recovery of side products indicated that **7** and two products of its further reaction, **8** and **9**, totaled approximately 30% of the reaction mixture. These observations suggested a low regioselectivity of approximately 2:1 in the first epoxide-opening cyclization, which contradicted our initial supposition that regioselectivity is similar in each ring-forming event.[2a] The nearly constant yield per epoxide opening that formed the basis of our original supposition is, in fact, an arithmetic coincidence.

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[3] *original references:* (a) Bloch, K.; Rittenberg, D. *J. Biol. Chem.* **1945**, *159*, 45. (b) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (c) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta.* **1955**, *38*, 1890. (d) Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191. *more recent reviews and perspectives:* (e) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011. (f) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730. (g) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2812.

[4] *selected original reports:* (a) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917. (b) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586. *accounts:* (c) Valentine, J. C.; McDonald, F. E. *Synlett* **2006**, 1816. (d) McDonald, F. E.; Tong, R.; Valentine, J. C.; Bravo, F. *Pure Appl. Chem.* **2007**, *79*, 281.

[5] Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915.

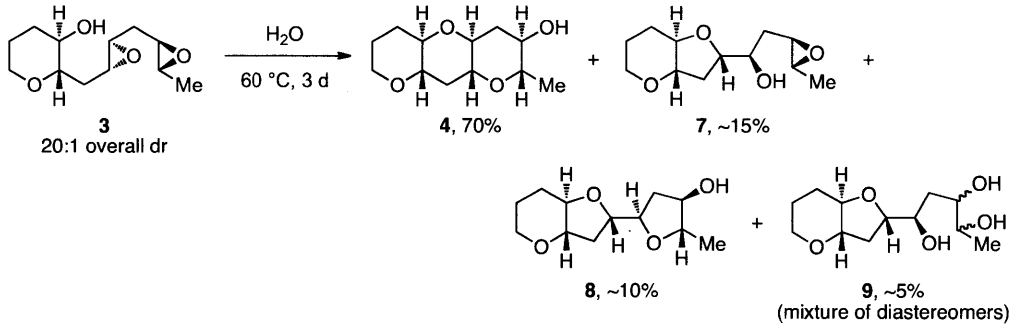
[6] (a) Tanuwidjaja, J.; Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084. (b) Underwood, B. S. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 2010.

[7] (a) Nakanishi, K. *Toxicon* **1985**, *23*, 473. (b) Lee, M. S.; Qin, G.-w.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234.

[8] Shimizu, Y. In *Natural Toxins: Animal, Plant, and Microbial*; Harris, J. B., Ed.; Clarendon: Oxford, 1986; p. 123.

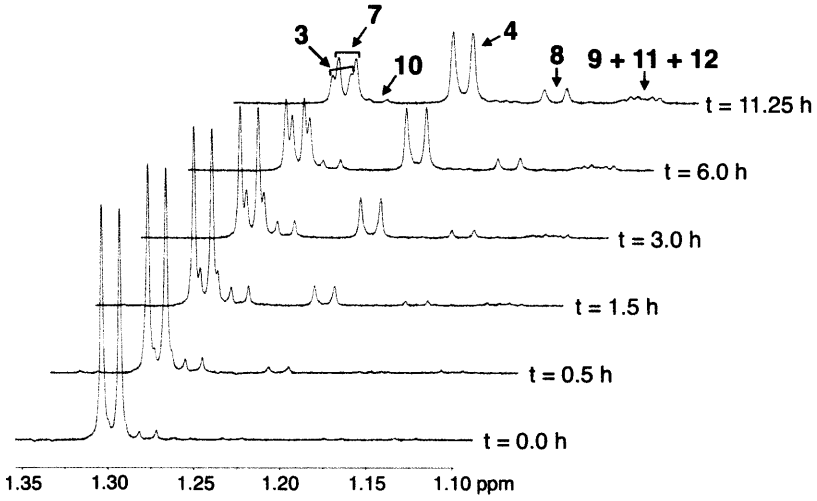
[9] Dr. Ivan Vilotijevic had earlier observed the formation 6,5-fused epoxy alcohol **7** in the water-promoted cascade reaction of diepoxide **3**; see ref. 2a.

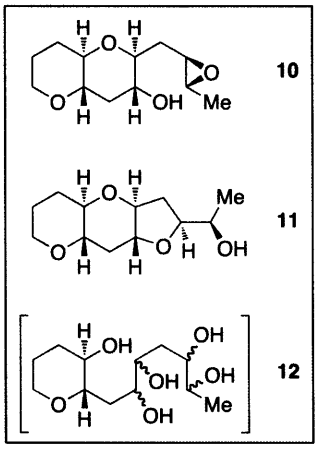
Scheme 2. Reaction of diepoxy alcohol **3** in water.



Intrigued, we elected to monitor the reaction of diepoxide **3** *in situ* by ^{1}H NMR spectroscopy (D_2O, 70°C, buffered to pD 7 with potassium phosphate). As in our previous study of monoepoxide **1**, we were pleased to find that the signals corresponding to the methyl substituents of relevant species in the reaction were mostly distinct and diagnostic (Figure 1). We were able to assign the resonances of starting diepoxide **3** (1.310 ppm) and desired THP triad **4** (1.240 ppm). A number of other peaks were visible. Three of these corresponded to the previously isolated *exo* side product **7** (1.306 ppm), its 5-*endo* cyclization product, 6,5,5-tricycle **8** (1.186 ppm), and its hydrolysis products **9** (1.140 and 1.141 ppm). Early in the reaction ($t \leq 6$ h), one other major resonance was plainly visible, labeled as **10**. We hypothesized that species **10** might be a THP diad, the intermediate in a two-step cascade of cyclizations from diepoxide **3** to triad **4**.

Figure 1. Upfield region of ^{1}H NMR spectra from reaction of **3** in D_2O at 70 °C and pD 7.0 (0.1 M KP_i buffer).





B. Synthesis of reactive intermediates and side products from the cascade reaction of 3.

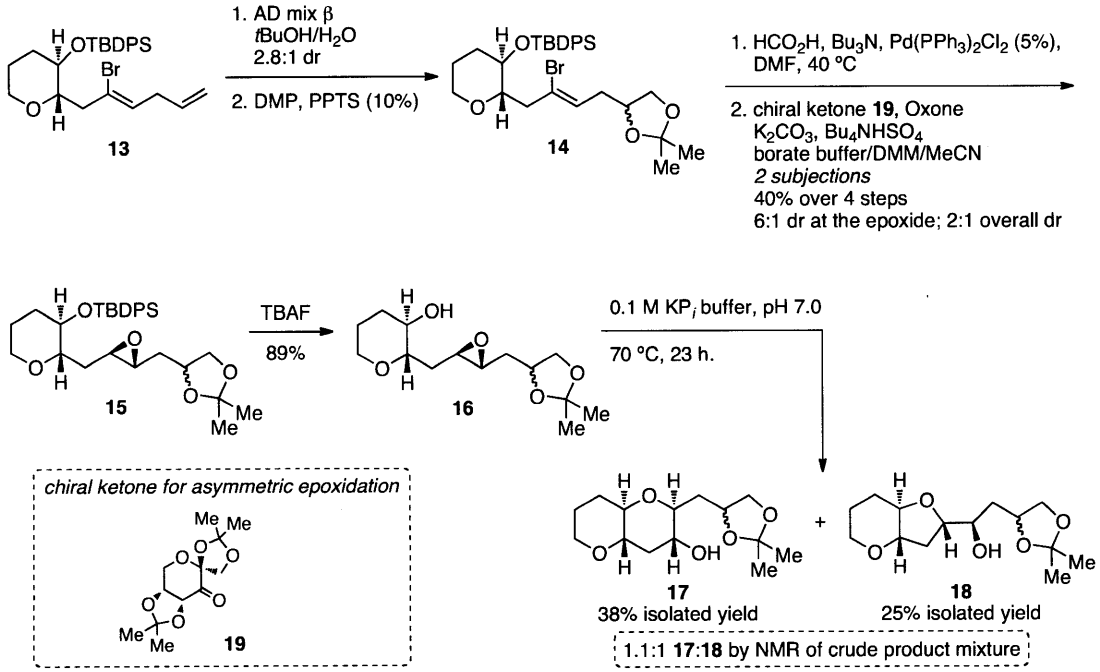
While we hypothesized that unknown intermediate **10** might be the THP diad-templated epoxy alcohol, we had no authentic sample of the compound. We thus opted to prepare it independently. Synthesis of side products **7**, **8**, and **9** confirmed their structures as well.

Synthesis of all of these compounds commenced from previously prepared alkenyl bromide **13** (see Chapter II for details). The more electron rich olefin of **13** was chemoselectively 1,2-dihydroxylated via Sharpless's asymmetric dihydroxylation protocol[10] (Scheme 3). The resulting diol, a mixture of diastereomers, was protected with dimethoxypropane to provide acetonide **14**. Alkenyl bromide **14** was reduced with formate and catalytic Pd to provide the *trans*-disubstituted olefin,[11] which was then

[10] (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
[11] (a) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821. (b) Xu, J.; Burton, D. J. *J. Org. Chem.* **2005**, *70*, 4346.

subjected to Shi's asymmetric epoxidation reaction[12] to furnish epoxide **15**. Desilylation of **15** with TBAF afforded alcohol **16**.

Scheme 3. Synthesis of 6,6-fused intermediate **17** and 6,5-fused intermediate **18**.



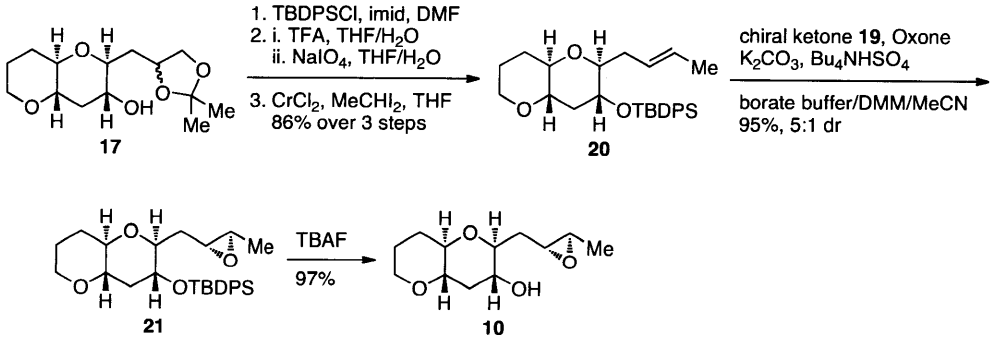
Epoxy alcohol **16** cyclized upon heating to 70 °C in pH 7 buffer, to provide 6,6-fused *endo* product **17** and 6,5-fused *exo* product **18** (Scheme 3). The acetonides of **16**, **17**, and **18** survived the 23 hour reaction period. Heating was found to be necessary to drive the reaction to completion; after stirring **16** in deionized water at ambient temperature for 3 days, only about 30% conversion was obtained. At 1.1:1, the *endo*:*exo* selectivity of the cyclization of **16** was dramatically lower than the 10:1 observed in the comparable water-promoted cyclization of epoxy alcohol **1** (Scheme 1). Similarly poor regioselectivity was observed on cyclization of **16** at pH 6 and pH 8. The reduced regioselectivity must be attributed to the pendent diol unit, which replaces the methyl group of **1**. We hypothesize that the difference is both electronic and conformational in origin. The electronic effect is an inductive electron-withdrawing one, which destabilizes the development of positive charge at the *endo* site of attack in **16**. As we have substantial evidence for some epoxonium character in the transition states in water-

[12] (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.

promoted cyclization (see Chapters I and II), this factor will erode *endo* selectivity. In concert with an electronic effect, the acetonide substituent could also undermine regioselectivity by interfering with the network of hydrogen-bonded water molecules stabilizing the transition state to *endo* cyclization. We later discovered that a similar diminishment in regioselectivity is incurred upon replacing the protected diol unit of **16** with an epoxide, as in diepoxide **3**. We offer a more detailed hypothesis of why these substituents may erode *endo* selectivity in Section D below.

THP diad **16** was converted to epoxy alcohol **10** in five steps (Scheme 4). Protection of the alcohol as its TBDPS ether, deprotection of the acetonide, and oxidative cleavage of the free vicinal diol with $NaIO_4$ provided the aldehyde, which was then transformed to *trans*-disubstituted alkene **20** via Takai olefination.[13] Shi epoxidation of **20** gave epoxide **21**, and treatment with TBAF finally furnished epoxy alcohol **10**, the presumed intermediate in a stepwise *endo*-selective cascade reaction of diepoxide **3**.

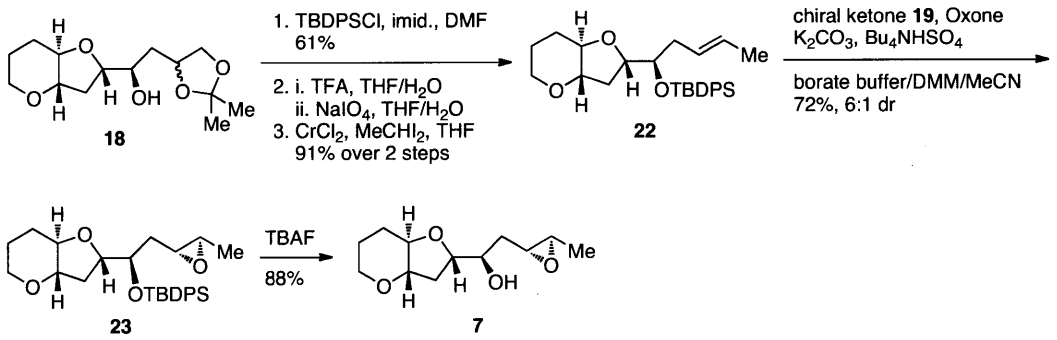
Scheme 4. Synthesis of THP-diad templated epoxy alcohol **10**.



The *exo* side products from the cascade reaction of **3**, compounds **7**, **8**, and **9** (Scheme 2), were all prepared from 6,5-fused intermediate **18** through a similar sequence. As before, compound **18** was protected as its TBDPS ether (Scheme 5). Removal of the acetonide and oxidative cleavage of the resulting free diol then gave the aldehyde, which was olefinated under Takai's protocol to provide alkene **22**. Shi epoxidation afforded **23**, and cleavage of the silyl ether then yielded epoxy alcohol **7**.

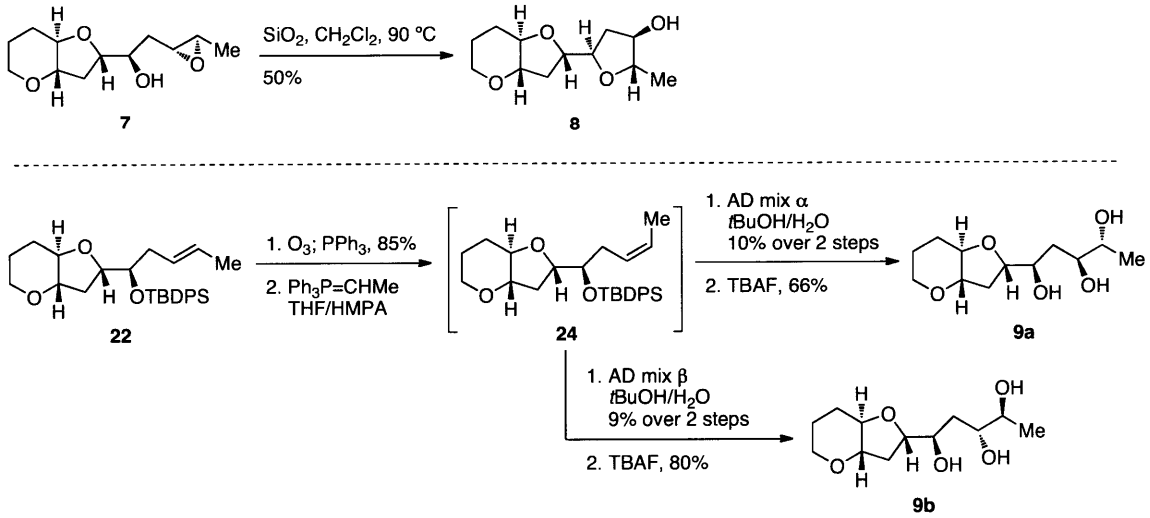
[13] Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951.

Scheme 5. Synthesis of 6,5-fused epoxy alcohol **7**.



THF side product **8** was prepared from silica gel-promoted 5-*endo* cyclization of epoxy alcohol **7**[14] (Scheme 6). Diastereomeric triols **9a** and **9b** were prepared from alkene **22**. Ozonolysis of **22** regenerated the aldehyde, which was then subjected to *Z*-selective Wittig olefination[15] to provide *cis*-disubstituted olefin **24**. Sharpless asymmetric dihydroxylation (SADH) of **24** with both enantiomers of the AD mix reagent mixture and subsequent desilylation with TBAF then provided **9a** and **9b**. Isolated yields of **9a** and **9b** were surprisingly low, given the generally good yields obtained from Wittig olefination and SADH. These reactions are unoptimized, and it is possible that one contributing factor was low recovery of the polar diols from aqueous extraction.

Scheme 6. Synthesis of 6,5-fused side products **8** and **9**.



[14] Van Dyke, A. R.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 4430.
[15] Denmark, S. E.; Senanayake, C. B. W. *Tetrahedron* **1996**, *52*, 11579.

C. Kinetic analysis of the water-promoted cascade reactions of diepoxy alcohol 3 and epoxy alcohols 7 and 10.

Now armed with compounds **4**, **7**, **8**, **9**, and **10**, we acquired ^{1}H NMR spectra of each in D_2O at 70 °C, as references for kinetics experiments. Characterization of epoxy alcohol **10** confirmed its transient presence in the water-promoted cascade reaction of diepoxy alcohol **3**. These results implied that formation of THP triad **4** could proceed in a stepwise fashion, but it remained to be shown that THP diad **10** represents a chemically and kinetically competent intermediate. The proposed stepwise mechanism was thus corroborated with a full kinetic analysis of the cascade reaction of **3** and the cyclization reaction of **10**.

We return to the ^{1}H NMR spectra of the reaction of diepoxy alcohol **3** in D_2O (Figure 1). All of the following kinetics experiments were planned, executed, and analyzed in collaboration with Dr. Jeffery A. Byers of the Jamison group. During the reaction of **3**, the concentrations of **4**, **8**, and **10** could be determined directly from integration of the ^{1}H NMR peaks corresponding to their methyl groups (Figure 1). Although the doublets corresponding to diepoxide **3** and *exo* intermediate **7** overlapped, the concentrations of **3** and **7** could be deduced simply by allocating the combined integration in proportion to their relative peak heights. A cluster of peaks was observed around 1.15 ppm, including those corresponding to diastereomeric triols **9**. These overlapping resonances proved more difficult to dissect. One of the components of this cluster was ultimately revealed to be undesired 6,6,5-fused tricycle **11** after independent preparation and characterization of the compound (*vide infra*). Another component, designated **12**, could not be isolated cleanly and is tentatively assigned as a mixture of diastereomeric, highly polar pentaols arising from exhaustive hydrolysis of the epoxides of **3** (Scheme 7, *vide infra*). Because of the complexity of the overlapping peaks, as well their low combined integration (less than 10% of total concentration, even after three half-lives), we were unable to apportion [**9**], [**11**], and [**12**] according to peak height, as was possible with [**3**] and [**7**].

We were therefore obliged to determine [**11**] via an alternative method, gas chromatography. Samples of **3** that had been followed by ^{1}H NMR spectroscopy through three half-lives were then exhaustively heated to 70 °C for 5 days so that the reaction mixture contained < 1% of epoxide intermediates **7** and **10**.[16] At this point, the ratio of [**4**]:[**11**] was determined to be 15:1 by GC. With the assumption that **4** and **11** are both derived from **10** and that selectivity ($k_6^{\mathbf{10}}:k_5^{\mathbf{10}}$) for their formation is constant at 15:1,[17] [**11**] could then be estimated from [**4**].

A representative graph of the concentrations of all species as a function of time thus obtained is shown in Figure 2. As expected, consumption of diepoxide **3** displayed pseudo-first order kinetics. Consistent with the assignment of **7** and **10** as reactive intermediates, their concentrations initially increased and then decreased over time. Interestingly, intermediate **10** was much shorter-lived than **7**, which remained a major species in solution even after 12 h. at 70 °C. We also observed a significant induction period for the appearance of product **4**, which is consistent with its formation from **10** and a hallmark of a stepwise reaction mechanism.[18] Finally, it is noteworthy that the overall concentration of starting material, intermediates, and products remained constant to within 3% over the course of the reaction, as compared to a DMSO internal standard. This detail indicates that all species were fully dissolved and is consistent with our earlier studies of epoxide-opening cyclization promoted by water,[2b] which demonstrated that the reaction occurs in solution rather than on the surface of water or in micelles.

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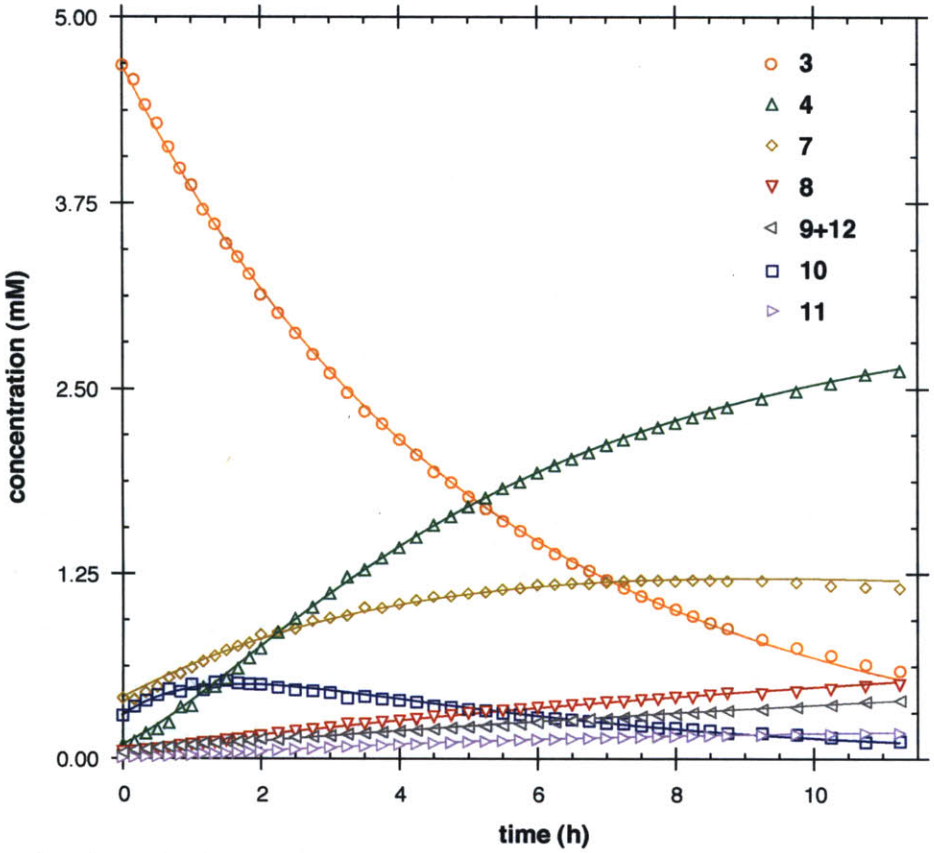
[16] GC analysis of incomplete reaction mixtures led to thermally-induced cyclization of remaining epoxide **3** and intermediates **7** and **10** in the GC inlet, thus leading to inaccurate measurements of selectivity.

[17] Our previous investigations indicate that epoxy alcohol cyclizations promoted by water are under kinetic control and that *endo*:*exo* regioselectivity does not change throughout the reaction; please see ref. 2b.

[18] Connors, K. A. *Chemical Kinetics*; VCH: New York, NY, 1990.

Figure 2. Concentrations of observable species over time in the cascade reaction of **3** in D_2O at 70 °C and pD 7.0. Symbols mark experimental data and solid lines represent the results of the rate equations derived from simulation, as presented in the mechanism in Scheme 7.



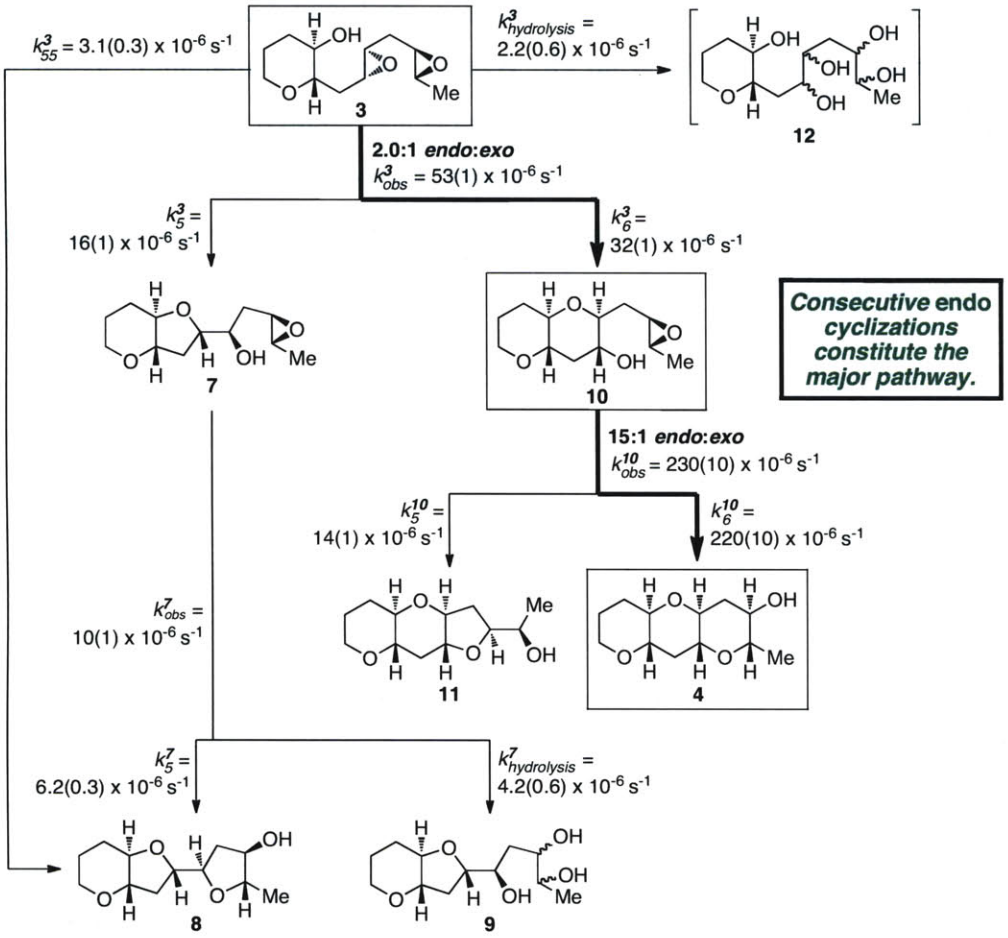
Having hypothesized a two-step mechanism from diepoxide **3** to THP triad **4** via monoepoxide **10**, Dr. Byers first determined rate constants for the elementary steps of the reaction sequence using direct nonlinear regression analysis.[18] Extraction of the rate constants for the consumption of **3** and **10** using this method was possible from concentration vs. time data, and the results fit fairly well with the independently measured rate constant for the cyclization of intermediate **10** (*vide infra*, Table 1). However, analogous kinetic analysis of the formation of side product **8** via the presumed intermediate **7** in a parallel stepwise cascade reaction that begins with *exo* cyclization of diepoxide **3** proved inconsistent with kinetic measurements carried out for cyclizations of independently prepared monoepoxide **7**. Particularly troubling was the relative

distribution of products **8** and **9**, which was different in cyclizations of the isolated monoepoxide **7** as compared to the cascade cyclization of **3** (*vide infra*).

Due to the sophisticated kinetic profile of the reaction, we turned to simulation of the experimental data with COPASI ("COmplex PAthways SImulator," an open-source software program for modeling chemical kinetics; see Experimental Section for details of the computation).[19] The results from Dr. Byers's optimized simulation appear as solid lines in Figure 2, and the associated rate constants are reported in Scheme 7 and Table 1. To reiterate, the curves shown are not simply the best statistical fit using nonlinear regression analysis but rather the results predicted from the rate laws that were derived from computer simulation.

[19] COPASI (Complex Pathway Simulator) 4.5: Hoops, S.; Sahle, S.; Gauges, R.; Lee, C.; Pahle, J.; Simus, N.; Singhal, M.; Xu, L.; Mendes, P.; and Kummer, U. *Bioinformatics* **2006**, *22*, 3067.

Scheme 7. Proposed mechanism of the water-promoted epoxide-opening cascade reaction of **3** (D_2O, pD 7, 70 °C). (Rate constants reported are the average results for simulation of experimental data for three independent experiments. The average error over the three experiments is shown in parentheses.)



Optimization of the simulation to achieve good agreement with experimental data ultimately took several iterations, as is discussed in the following paragraphs. Nevertheless, an immediately striking feature of the results of both regression analysis and simulation were the low rate and regioselectivity of the first cyclization of diepoxide **3**. Simulation indicates that diepoxide **3** reacts at approximately 1/5 the rate of the monoepoxide model system **1** ($k^3_{obs} = 53 \times 10^{-6}$ s^{-1} vs. $k^1_{obs} = 290 \times 10^{-6}$ s^{-1})[2b] and cyclizes with significantly lower *endo* selectivity ($k^3_6 : k^3_5$ = 2.0:1 vs. $k^1_6 : k^1_5$ = 11:1). In contrast, the rate of cyclization of THP diad **10** is similar to that of **1** ($k^{10}_{obs} = 230 \times 10^{-6}$ s^{-1}), and the

cyclization occurs with somewhat higher *endo* selectivity (k_6^{10}:k_5^{10} = 15:1). Notably, both 5-*exo* cyclization reactions occur at similar, slow rates (k_5^3 and $k_5^{10} < 20\times10^{-6}$ s^{-1}). 6-*Endo* cyclization of **3** is somewhat faster ($k_6^3 = 32\times10^{-6}$ s^{-1}), and 6-*endo* cyclization of **10** ($k_6^{10} = 220\times10^{-6}$ s^{-1}) is much faster still, thus explaining the observations that the concentration of intermediate **10** never exceeded 10% of the total reaction mixture and that **4** is the major product of the reaction (Figure 2).

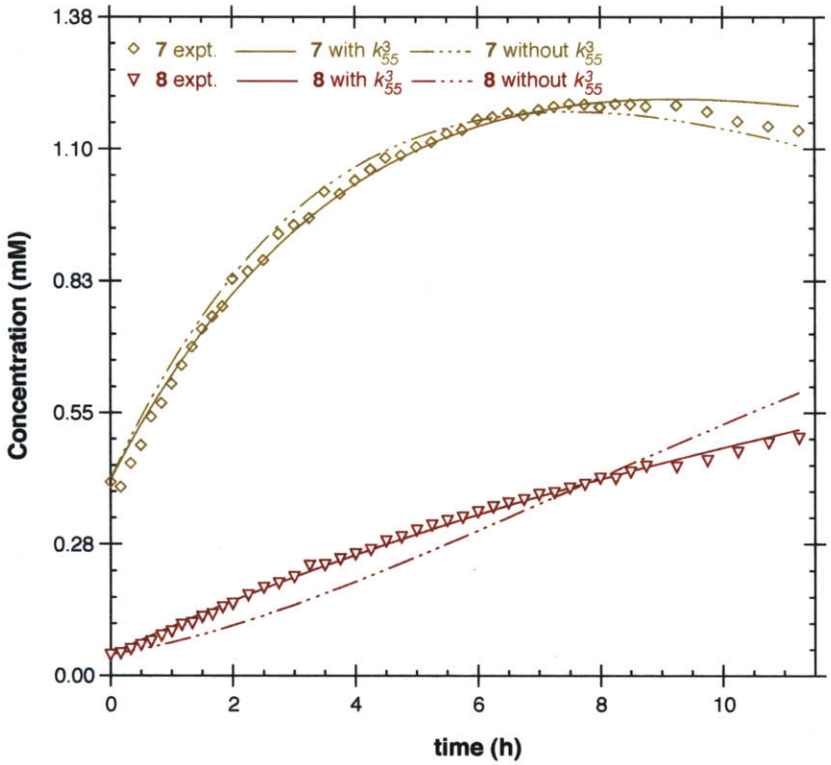
To corroborate that THP diad **10** is a kinetically competent intermediate, the kinetics of the cyclization of independently synthesized **10** in D_2O at 70 °C were measured. Consistent with our mechanistic hypothesis, the disappearance of **10** proceeded with clean pseudo-first order kinetics to produce **4** as the major product. Only a trace of the *exo* product, 6,6,5-fused triad **11**, was observed as the sole side product of the reaction. Importantly, both reaction rate ($k_{obs}^{10} = 270\times10^{-6}$ s^{-1}) and regioselectivity (k_6^{10}:k_5^{10} = 19:1) were closely comparable to those determined from simulation of the cascade reaction of diepoxide **3** (Table 1), thereby definitively demonstrating that monoepoxide **10** is a competent intermediate en route to THP triad **4**.

We also measured the kinetics of the reaction of 6,5-fused epoxy alcohol **7** under the same conditions. Consistent with its long lifetime in the cascade reaction mixture, epoxy alcohol **7** reacted much more slowly than **10** ($k_{obs}^7 = 11.5\times10^{-6}$ s^{-1}). As expected, **7** was converted to 6,5,5-triad **8** and hydrolysis products **9**, a mixture of diastereomers.[20] However, a critical discrepancy between this reaction and the cascade reaction was revealed: the ratio of **8** to **9** proved to be lower in the reaction of isolated **7** than in the cascade reaction of diepoxide **3** ([**8**]:[**9**] = 0.56:1 in the reaction of isolated **7** vs. [**8**]:[**9**+**12**] ~ 1.5:1 in the reaction of **3**). This observation suggested the existence of a competing mechanism for the formation of 6,5,5-tricycle **8** during the cascade reaction of diepoxide **3**, one that directly converts **3** to **8**. Support for this additional pathway came from simulation of the cascade reaction of **3**, which generated poor correlations between simulated and experimental data for [**7**] and especially [**8**] when a direct pathway from **3**

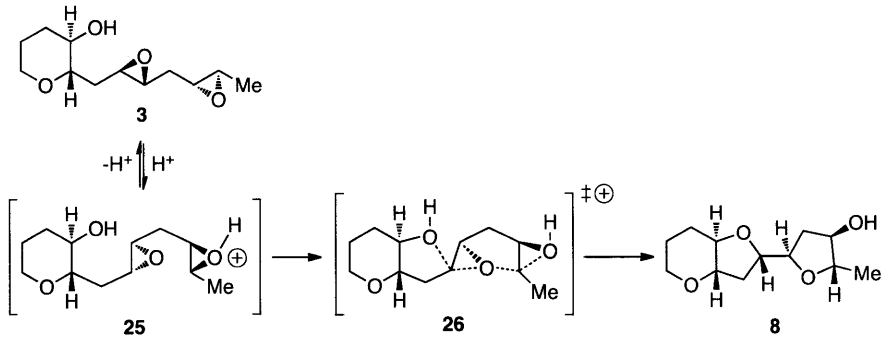
[20] Other unidentified products were also observed during the cyclization of isolated **7**, which account for nearly 30% of the consumption of **7** and explain the difference between k_{obs}^7 and ($k_{hydrolysis}^7 + k_5^7$). The same unknown compounds were observed in trace amounts in the cascade reaction of **3**, where they constitute only about 1% of total concentration after three half lives. These species were ignored in the kinetic analysis.

to **8** was excluded from the model (Figure 3). With the inclusion of a simulated rate constant for a direct pathway from **3** to **8** ($k_{55}^{3} = 3.1 \times 10^{-6}$ s^{-1}), good correlation was achieved. We estimate that about 6% of diepoxide **3** is lost to the direct pathway from **3** to **8**. We surmise that this cascade pathway is acid-promoted (possibly by trace hydronium present at pD 7) and therefore likely occurs through a concerted mechanism (Scheme 8).[4,5]

Figure 3. Comparison of simulated data to experimental data in the reaction of diepoxide **3**, showing fit between the two *with* and *without* k_{55}^{3}, a direct pathway from **3** to **8**, included in the simulation. Symbols mark experimental data and lines show simulated curves.



Scheme 8. Proposed concerted, acid-catalyzed pathway from **3** to **8**.



A final refinement to the simulation was the inclusion of $k^3_{hydrolysis}$, a direct hydrolysis pathway from **3** to the presumed pentaols **12** (Scheme 2). The addition of this last pathway made a minor but still significant improvement to the agreement between simulation and experimental data, affording a good fit for each species (Figure 2). Rate constants for each step of the cascade, as determined from this optimized simulation, are presented in Scheme 2 and Table 1. We posit that it is the presence of the small but non-negligible $k^3_{hydrolysis}$ and k^3_{55} that account for the imperfect agreement between the experimental data and the rates determined from direct analytical regression, which assumes parallel two-step processes void of any competing one-step side reaction pathways. Computer simulation, however, does not require this assumption.

Table 1. Comparison of rate constants determined from the cascade reaction of **3** and from reactions of isolated **7** and **10**. Values shown in parentheses are the average absolute error for three independent measurements. All experiments were conducted in D_2O at 70 °C and pD 7.0.

		as determined from isolated reaction of **10**	as determined from isolated reaction of **7**	as determined from direct regression analysis of cascade reaction of **3**	as determined from simulation of cascade reaction of **3**
k^3 (s^{-1} x 10^{-6})	k^3_{obs}	-	-	52 (2)	53 (1)
	$k^3_6 : k^3_5$	-	-	1.6	2.0
	k^3_{55}	-	-	-	3.1 (0.3)
	$k^3_{hydrolysis}$	-	-	-	2.2 (0.6)
k^{10} (s^{-1} x 10^{-6})	k^{10}_{obs}	270 (30)	-	183 (3)	230 (10)
	$k^{10}_6 : k^{10}_5$	19	-	15	15
k^7 (s^{-1} x 10^{-6})	k^7_{obs}	-	11.5 (0.1)	19.2 (0.4)	10 (1)
	$k^7_5 : k^7_{hydrolysis}$	-	0.56	1.3	1.5

D. Analysis of kinetics experiments.

To summarize our kinetic findings, the water-promoted *endo*-selective epoxide-opening cascade of **3** occurs via a stepwise mechanism. The first step proceeds with low rate and regioselectivity, while the second is a faster and exceptionally selective cyclization templated by a THP diad. Any direct, concerted mechanism from **3** to THP triad **4** is negligible. In fact, attempts to include this pathway in the COPASI simulation point to an upper limit of just 2 x 10^{-7} s^{-1}, which would represent much less than 1% of the reaction of **3**.

Continuing efforts are aimed toward understanding why selectivity and rate differ in the two steps of the cascade reaction. The cyclization of **3**, which is much slower and less regioselective than the cyclization of either **1** or **10**, is especially peculiar. We hypothesize that the origins of this difference could be both enthalpic and entropic in nature. An enthalpic explanation would invoke some epoxonium character in the transition state to *endo* cyclization. If during cyclization of **3** there is some development of positive charge on the epoxide being opened, then the inductive electon-withdrawing

effect of the adjoining second epoxide could destabilize the incipient positive charge at the *endo* site of attack, thereby eroding regioselectivity. While this explanation conveniently rationalizes the improved regioselectivity of the second step, where a neighboring inductive electron-withdrawing group is absent, our current mechanistic understanding of the cyclization of **1** suggests that entropic rather than enthalpic factors dictate selectivity.[2b] Consistent with an entropically controlled reaction is the observation that regioselectivity is relatively insensitive to temperature.[2] Therefore, entropic factors, including differences in the ground state and transition state conformations of **3** as compared to **1** or differences in solvent reordering for the two reactions, may be more important than any electron-withdrawing effect. The presence of the second epoxide, a substituent significantly longer and bulkier than a simple methyl group, may make organizing **3** into the compressed orientation required for *endo* cyclization more difficult than **1**, requiring a $\Delta S^{\ddagger}$ that is larger and more negative. Beyond its bulk, the second epoxide of **3** also brings an additional Lewis basic hydrogen bond acceptor into the system, which could perturb the network of water molecules solvating the ground state and reactive conformers of **3**. Any or all of these factors can alter the trajectory of nucleophilic approach to the epoxide, a factor which computational studies have shown to be most important in dictating regioselectivity in epoxy alcohol cyclizations.[21]

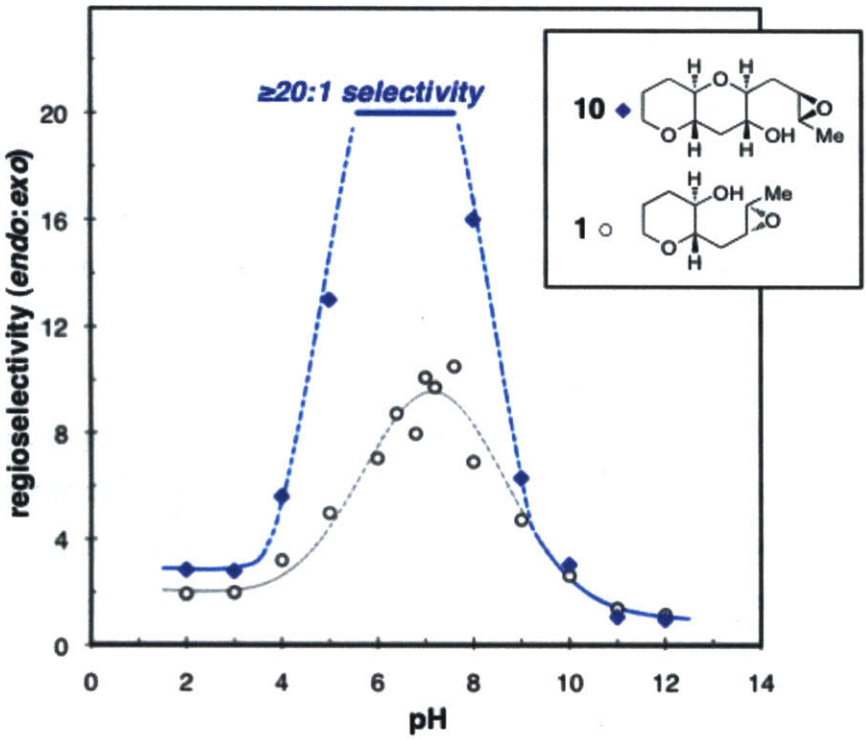
E. Further investigation of epoxy alcohol 10. Elucidation of a powerful THP diad template.

While the first cyclization step of **3** is rather poor, the water-promoted cyclization of THP diad-templated epoxy alcohol **10** is remarkably efficient. Although cyclizations of **10** and **1** exhibit similarly low regioselectivities in basic and acidic water,[2a] cyclizations of **10** in neutral water at room temperature displayed substantially higher endo selectivity (greater than 20:1, the limit of detection) than the analogous reactions of **1** (Figure 4). Apparently, the combination of THP diad **10** and neutral water engenders a more powerful template effect than the single THP ring of **1**. Here again we propose that

[21] (a) Na, J.; Houk, K. N.; Shevlin, C. G.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 8453. (b) Coxon, J. M.; Thorpe, A. J. *J. Org. Chem.* **1999**, *64*, 5530.

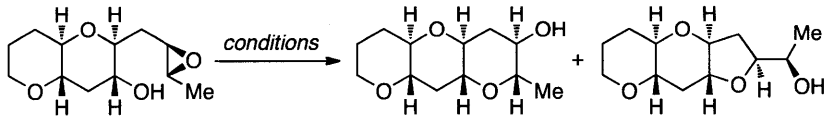
the essential distinction is conformational, arising from the greater rigidity and increased number of hydrogen bond acceptors inherent to the 1,6-dioxadecalin template of **10**.

Figure 4. Dependence of regioselectivity on pH for cyclizations of **1**[2a] and **10** (room temperature, 0.1 or 1.0 M KP_i buffer).



Unlike cyclization in neutral water, cyclization of THP diad-templated epoxy alcohol **10** under acidic and basic activation in organic solvent proceeded with low regioselectivity. Measured selectivity values were very similar to those observed for THP-templated **1**[2a,c] (Table 2, entries 1-3). This observation again suggests that the high regioselectivity of cyclization of **10** in neutral water is a primarily conformational and entropic effect. If the second THP ring were somehow exerting a long-range electron-withdrawing effect rather than a conformational one, then one would expect to see higher *endo* selectivity under activation by acids BF_3 and CSA.

Table 2. Cyclization of epoxy alcohol **10** upon activation by acid and base.



10 *endo* (**4**) *exo* (**11**)

entry	promoter/solvent [a]	T (°C)	time	regioselectivity (**4**:**11**) [b]
1	Cs_2CO_3 (30 equiv), MeOH	rt	18 h	0.64:1
2	(+/-)-CSA (1 equiv), CH_2Cl_2	rt	18 h	1.4:1
3	BF_3•OEt_2 (25 mol%), CH_2Cl_2	-78 to rt	30 min	1.5:1
4	deionized H_2O	rt	19 d	>20:1
5	D_2O (pD 7, 0.1 M KP_i buffer)	70	24 h	19:1

[a] All reactions were run at 0.02 M and to >98% conversion of **10**.
[b] Regioselectivity determined by ^{1}H NMR spectroscopy. Results are the average of at least 2 experiments.

F. Conclusion

The study of the reaction of diepoxy alcohol **3** to THP triad **4** presented above provides experimental evidence that *endo*-selective epoxide-opening cascade reactions promoted by water proceed by a stepwise mechanism rather than through a concerted process. NMR analysis provides quantitative rate information for both steps of the major pathway as well as for unproductive side reaction pathways. Independent preparation and characterization of epoxy alcohol **10** confirm its intermediacy in the cascade reaction and reveal that its THP diad is a more powerful template than a single THP ring.

Importantly, this study does not support any significant contribution from a concerted pathway from **3** to **4**. The stepwise mechanism of this nucleophilic *endo*-selective epoxide-opening cascade promoted by water therefore appears to be fundamentally different from the synchronous mechanism proposed for cascade reactions involving electrophilic epoxonium openings.[4,5] We believe that this difference is further evidence that neutral water is acting as something other than a simple mild Brønsted acid. Rather, water is more likely to serve as a bifunctional promoter, one that activates both the hydroxyl and epoxide reactive partners through an extensive hydrogen bond network.

We surmise that longer cascades (three or more epoxides) in water (e.g., **5** to **6**, Scheme 1) also proceed via similar stepwise mechanisms. While we hesitate to speculate

too broadly about a potential connection between these experiments and the proposed biogenesis of the ladder polyethers,[7,8] it is interesting to consider that the first step in the cascade reaction of **3** is the most challenging; it proceeds with low rate and poor regioselectivity. If the appendage of more fused rings to the template makes subsequent cyclization steps faster and more selective, then epoxide-opening cyclizations promoted by neutral water may be more plausibly invoked as components of the biosynthesis of the ladder polyethers. However, as we have yet to demonstrate that any trend of increasing regioselectivity extends to cascades of more than two epoxides, this proposal remains an untested hypothesis.

Nevertheless, knowledge of the stepwise mechanism of water-promoted epoxide-opening cascades can be useful in the application and optimization of such cascades in target-directed synthesis. For example, the recognition that the more rigid THP diad template of **10** is especially effective may point to a strategy for the formation of medium rings via *endo*-selective epoxide opening cyclization, which remains a significant outstanding challenge. Even THP formation via 6-*endo* epoxide-opening cyclization is not yet a completely solved problem — in Chapter V, we describe a series of *endo*-selective epoxide-opening cascades applied to the synthesis *FGH* ring system of the ladder polyether gambierol. Lessons learned from the foregoing mechanistic study were essential in optimizing these reactions. A successful cascade requires emphasizing the desired stepwise, *endo*-selective cascade pathway at the expense of competing unselective acid-catalyzed pathways. In Chapter V, we describe how substituent effects can tilt this balance.

G. Experimental Section.

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Except where noted, dichloromethane, tetrahydrofuran (THF), Et_2O, and triethylamine were purified via an SG Water USA solvent column system. Anhydrous dimethylformamide (DMF) from Aldrich was used without further purification. Reactions in water used deionized water without further purification. Cyclization reactions carried out in Millipore water showed results identical to those in deionized water. Chiral ketone **19**, used in Shi asymmetric epoxidation, was prepared from D-fructose according to the procedure of Vidal-Ferran and coworkers.[22] 1,1-diiodoethane, used in Takai olefination, was prepared according to the procedure of Letsinger and Kammeyer.[23] All other reagents and solvents were used as obtained, without further purification.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ceric ammonium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). Analytical HPLC was performed on the column phase indicated on a Hewlett-Packard 1100 Series HPLC. Preparative HPLC was performed on the column phase indicated on an Agilent 1200 Series HPLC.

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR. High resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Jasco Model 1010 polarimeter at 589 nm.

^1H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded in $CDCl_3$, C_6D_6, or D_2O, as indicated, on a Varian Inova-500 MHz spectrometer, a Bruker AVANCE-400 MHz spectrometer, or a Bruker AVANCE-600 MHz spectrometer. Chemical shifts in routine ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual $CHCl_3$ in $CDCl_3$ (7.27 ppm), C_6HD_5 in C_6H_6 (7.15 ppm), or HOD in D_2O (4.79 ppm) (all at room temperature). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and app = apparent), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm), C_6D_6 (128.4 ppm), or, for carbon spectra in D_2O, from the resonance from an added drop of methanol (49.5 ppm),[24] on the δ scale. All kinetic data were determined by NMR using a Varian Inova-500 MHz spectrometer (*vide infra*).

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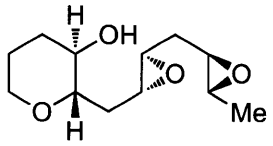
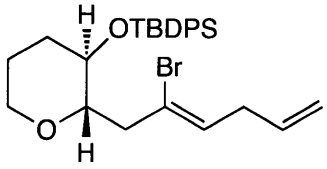
[22] Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143-10146.
[23] Letsinger, R. L.; Kammeyer, C. W. *J. Am. Chem. Soc.*, **1951**, *73*, 3376.
[24] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.



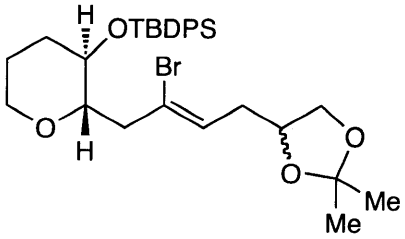
3

Diepoxide 3: This compound was prepared according to previously reported procedures; please see ref. 2a and Chapter II.



13

Alkenyl bromide 13: This compound was prepared according to previously reported procedures; please see Chapter II.



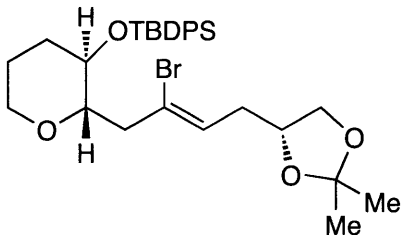
14

Acetonide 14: A commercial sample of AD mix β (984 mg) was dissolved in a mixture of *t*BuOH (3.5 mL) and H_2O (3.5 mL). This cloudy, bright orange solution was cooled to 4 °C. Meanwhile, skipped diene **13** (351 mg, 0.70 mmol) was dissolved in THF (700 μL), and this solution was cooled to 0 °C. After cooling, the solution of **13** was added to the AD mix, and the resulting suspension was stirred 27 h. at 4 °C. The reaction was then quenched with addition of solid Na_2SO_3 (1.06 g, 8.4 mmol). The mixture was warmed to room temperature and allowed to stir 30 min.; over this time, the color changed from vivid yellow-orange to a pale tan. The mixture was diluted with H_2O (~15 mL) and Et_2O (~30 mL). The aqueous layer was separated and extracted with Et_2O (2x~40 mL), and the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material (545 mg) was carried forward into acetonide protection without further purification. Major and minor diol diastereomers cospot; R_f = 0.45 (100% EtOAc) or 0.18 (50% EtOAc in hexanes).

This crude diol was dissolved in CH_2Cl_2 (1.45 mL) and 2,2-dimethoxypropane (1.04 mL,

874 mg, 8.4 mmol). Solid pyridinium *p*-toluenesulfonate (17.6 mg, 0.070 mmol) was added at room temperature, and the solution was stirred 23 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (2 mL) and diluted with H_2O (~5 mL) and CH_2Cl_2 (~5 mL). The aqueous layer was extracted three times with CH_2Cl_2 (20 mL each), and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude acetonide **14** as a pale yellow oil (400 mg). The crude product could be used without further purification. Major and minor diastereomers cospot; $R_f = 0.57$ (20% EtOAc in hexanes). However, a small portion of **14** was later purified for purposes of characterization. The diastereomers were inseparable by hand chromatography but could be purified away from other impurities (10% EtOAc in hexanes). The diastereomers could then be separated by preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5μm particle size, 25 cm length; 99.6:0.4 hexanes:*i*PrOH, 20 mL/min) to afford major diastereomer **14a** ($t_R = 8.3$ min.) and minor diastereomer **14b** ($t_R = 6.1$ min.). The diastereomeric ratio (d.r.) of crude **14** was found to be 2.8:1 by HPLC.

Please note: The stereochemical assignments of major diastereomer **14a** and minor diastereomer **14b** are made purely on the basis of Sharpless's rules for stereochemical induction in the asymmetric dihydroxylation of monosubstituted olefins.[10] The eventual destruction of the stereocenter in question makes this issue trivial, as the two diastereomers ultimately converge on a single product.



14a (major diastereomer)

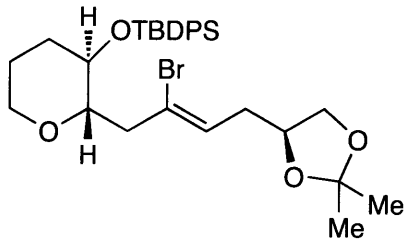
$[\alpha]^{22}_D = -13.4$ ($c = 0.70$, $CDCl_3$).

IR (thin film, NaCl) 2932, 2857, 1472, 1428, 1369, 1257, 1215, 1103, 1060 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.71-7.67 (m, 4H), 7.47-7.36 (m, 6H), 5.70 (app t, $J = 6.7$ Hz, 1H), 4.19 (app quintet, $J = 6.3$ Hz, 1H), 4.02 (dd, $J = 8.1$, 6.0 Hz, 1H), 3.81-3.75 (m, 1H), 3.60 (dd, $J = 8.0$, 7.2 Hz, 1H), 3.54-3.48 (m, 1H), 3.36 (app td, $J = 9.4$, 4.6 Hz, 1H), 3.31-3.25 (m, 1H), 3.12 (app d, $J = 14.7$, 1H), 2.58-2.51 (m, 1H), 2.49-2.42 (m, 1H), 2.22 (dd, $J = 14.8$, 10.1 Hz, 1H), 1.88-1.82 (m, 1H), 1.54-1.33 (m, 3H), 1.43 (s, 3H), 1.36 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.5, 133.7, 130.0, 130.0, 127.9, 127.7, 127.6, 125.7, 109.2, 80.1, 74.9, 72.0, 69.0, 67.9, 44.8, 35.8, 33.6, 27.2, 27.0, 25.9, 25.7, 19.5.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{41}BrO_4Si$ $(M+Na)^+$: 595.1850, found 595.1846.



14b (minor diastereomer)

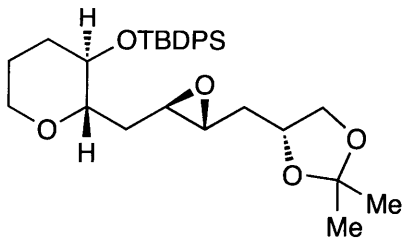
$[\alpha]^{22}_D$ = -3.4 (*c* = 0.23, CH_2Cl_2).

IR (thin film, NaCl) 2928, 2856, 1737, 1428, 1369, 1103 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H), 7.47-7.36 (m, 6H), 5.73 (app t, *J* = 6.8 Hz, 1H), 4.18 (app quintet, *J* = 6.4 Hz, 1H), 4.02 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.81-3.76 (m, 1H), 3.61 (dd, *J* = 7.9, 7.3 Hz, 1H), 3.53-3.48 (m, 1H), 3.36 (app td, *J* = 9.4, 4.6 Hz, 1H), 3.31-3.25 (m, 1H), 3.12 (app d, *J* = 14.9 Hz, 1H), 2.55-2.44 (m, 2H), 2.24 (dd, *J* = 14.7, 10.0 Hz, 1H), 1.88-1.81 (m, 1H), 1.58-1.34 (m, 3H), 1.42 (s, 3H), 1.36 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.5, 133.7, 130.0, 129.9, 127.9, 127.7, 127.7, 125.6, 109.2, 80.2, 74.9, 72.0, 69.0, 67.9, 44.8, 35.6, 33.6, 27.2, 27.0, 26.0, 25.7, 19.5.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{41}BrO_4Si$ $(M+Na)^+$: 595.1850, found 595.1841.



15

Epoxide 15: Crude alkenyl bromide **14** (400 mg, ~0.7 mmol) was dissolved in DMF (930 μL). A dry flask was charged with $Cl_2Pd(PPh_3)_2$ (24.6 mg, 0.035 mmol), to which was added the solution of **14** in DMF. To this lemon yellow solution was added Bu_3N (389 mg, 500 μL, 2.1 mmol) and then HCO_2H (64 mg, 53 μL, 1.4 mmol). The reaction solution smoked upon addition of the formic acid. It was stirred 15 min. at room

temperature, during which time it turned brown, then warmed to 40 °C for 41 h. The solution was then cooled to room temperature and filtered through a short pad of SiO_2 using 15% EtOAc in hexanes as an eluent to give a brown oil. NMR analysis of the crude reaction mixture revealed a 63:37 mixture of disubstituted alkene (the reduced product) and unreacted **14** (product cospots with **14** by TLC, $R_f = 0.59$ (20% EtOAc/hexanes)).

To this crude mixture in a mixture of dimethoxymethane (DMM)/MeCN (2:1 v/v, 56 mL) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M Na_2EDTA (38 mL), nBu$_4HSO_4$ (115 mg, 0.34 mmol), and chiral ketone **19** (346 mg, 1.34 mmol). The biphasic mixture was stirred vigorously at 0 °C while Oxone (4.1 g, 6.7 mmol) in 4 x 10^{-4} M aqueous Na_2EDTA (18.8 mL) was added simultaneously with an aqueous solution of K_2CO_3 (0.89 M, 18.8 mL, 16.8 mmol) via syringe pump addition over 30 minutes. The resulting mixture was stirred an additional 30 min at 0 °C, at which point it was diluted with EtOAc (~100 mL) and water (~50 mL). The aqueous layer was separated and extracted three times with EtOAc (100 mL each). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. NMR and TLC evidence at this point indicated approx. 35% conversion of the alkene. The reaction mixture was then resubjected to identical epoxidation conditions and worked up as before. Resubjection afforded approx. 80% overall conversion to epoxide **15**. The product was purified by column chromatography using a gradient of solvents (10% to 20% EtOAc in hexanes) to provide **15**, a colorless oil, as an inseparable mixture of diastereomers (207 mg of a 6:1 mixture of diastereomers at the epoxide (~2:1 overall d.r.), 0.305 mmol combined, 40% over 3 steps, $R_f = 0.50$ (25% EtOAc/hexanes)) as well as an inseparable mixture of vinyl bromide **14** (37 mg, 0.065 mmol) and the disubstituted alkene (59 mg, 0.119 mmol), R_f = 0.62 (25% EtOAc in hexanes). Epoxide **15** could be further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.6% *i*PrOH in hexanes, 20 mL/min.; t_R of major diastereomer = 12.4 min.) to afford **15** in a d.r. of 20:1, which was characterized.

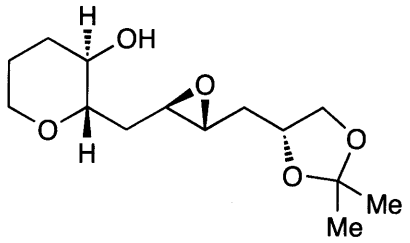
$[\alpha]^{22}_D = -15.0$ ($c = 0.10$, $CDCl_3$).

IR (thin film, NaCl) 3072, 2931, 2857, 1732, 1472, 1428, 1369, 1260, 1214, 1103 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.46-7.41 (m, 2H), 7.41-7.36 (m, 4H), 4.26 (app quint, J = 6.4 Hz, 1H), 4.09 (dd, J = 8.1, 6.0 Hz, 1H), 3.83-3.79 (m, 1H), 3.60 (app t, J = 7.7 Hz, 1H), 3.40 (app td, J = 9.2, 4.4 Hz, 1H), 3.33-3.27 (m, 2H), 2.82 (app td, J = 5.7, 2.1 Hz, 1H), 2.77 (ddd, J = 6.9, 4.2, 2.2 Hz, 1H), 2.03 (ddd, J = 14.3, 6.0, 2.6 Hz, 1H), 1.95 (ddd, J = 13.9, 6.7, 4.3, 1H), 1.84-1.79 (m, 1H), 1.67 (ddd, J = 14.3, 8.9, 5.4, 1H), 1.61-1.53 (m, 2H), 1.50-1.40 (m, 5H), 1.39 (s, 3H), 1.03 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 136.1, 134.7, 133.6, 130.0, 129.8, 127.9, 127.7, 109.0, 80.9, 74.0, 72.3, 69.5, 67.8, 56.9, 55.0, 36.6, 34.8, 33.5, 27.2, 27.1, 25.9, 25.6, 19.5.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{42}O_5Si$ $(M+Na)^+$: 533.2694, found 533.2692.



16

Epoxy alcohol 16: To a solution of silyl ether **15** (2.10 g, 4.1 mmol) in THF (6 mL) was added tetrabutylammonium fluoride (TBAF, 1M in THF, 8.2 mL, 8.2 mmol). The reaction was warmed to 40° for 2 h., cooled, and applied directly to a column of SiO_2. The SiO_2 was packed with 25% EtOAc in hexanes to which had been added 2% Et_3N, and the column was run with a gradient from 25% EtOAc in hexanes to 100% EtOAc to afford alcohol **16** as a pale yellow oil (990 mg, 3.6 mmol, 89%, $R_f = 0.51$ (EtOAc)).

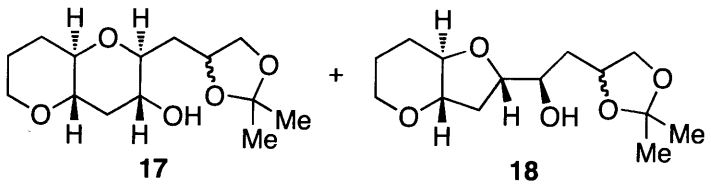
$[\alpha]^{22}_D = +10.9$ ($c = 0.095$, CH_2Cl_2)

IR (thin film, NaCl) 3427, 2924, 2853, 1653, 1456, 1370, 1213, 1159, 1094, 1058 cm^{-1}.

^1H NMR (600 MHz, C_6D_6) δ 4.04 (app dq, $J = 7.3, 5.8, 5.8, 5.8$ Hz, 1H), 3.78 (dd, $J =$ 8.1, 6.0 Hz, 1H), 3.71-3.67 (m, 1H), 3.47-3.40 (m, 1H), 3.36 (app t, $J = 7.6$ Hz, 1H), 3.08 (ddd, $J = 9.0, 5.6, 3.5$ Hz, 1H), 3.06-3.00 (m, 1H), 2.97 (ddd, $J = 6.7, 4.0, 2.2$ Hz, 1H), 2.67 (ddd, $J = 6.9, 4.2, 2.2$ Hz, 1H), 1.98 (app dt, $J = 14.7, 3.8$ Hz, 1H), 1.90-1.83 (m, 2H), 1.73 (ddd, $J = 14.6, 7.0, 5.8$ Hz, 1H), 1.65 (ddd, $J = 13.7, 7.8, 4.3$ Hz, 1H), 1.47-1.37 (m, 4H), 1.32 (s, 3H), 1.29-1.16 (m, 3H);

^{13}C NMR (100 MHz, C_6D_6) δ 109.3, 81.3, 74.2, 70.3, 69.9, 68.1, 56.3, 55.9, 37.2, 35.6, 33.2, 27.6, 26.5, 26.3.

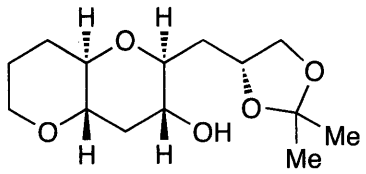
HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_5$ $(M+Na)^+$: 295.1516, found 295.1527.



17 **18**

THP diad 17 and 6,5-fused 18: Epoxy alcohol **16** (990 mg, 3.6 mmol) was dissolved in 0.1 M potassium phosphate buffer (pH = 7.0, 180 mL) and the resulting slightly cloudy solution was heated to 70 °C for 23 h. The solution was then cooled to room temperature

and extracted four times with EtOAc (400 mL each). The combined organics were washed with a small amount of brine (~30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture indicated an approximately 1.1:1 ratio of **17**:**18**. The mixture was purified by column chromatography using a gradient of solvents (50% to 100% EtOAc/hexanes), which resulted in fractions containing pure **17** (380 mg, 1.40 mmol, 38%, R_f = 0.52 (100% EtOAc)) and **18** (252 mg, 0.93 mmol, 25%, R_f = 0.44 (100% EtOAc)), along with fractions containing a significant quantity of both products (344 mg, 1.26 mmol, 35%).



17 (characterization of major diastereomer only)

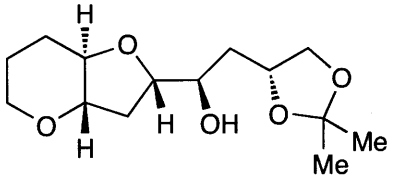
$[\alpha]^{22}_D$ = -17.9 (*c* = 0.13, CH_2Cl_2).

IR (thin film, NaCl) 3428, 2926, 2852, 1723, 1454, 1370, 1219, 1095, 1060, 1026 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.36 (dddd, *J* = 7.8, 7.7, 6.2, 4.1 Hz, 1H), 4.09 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.94-3.90 (m, 1H), 3.67-3.61 (m, 1H), 3.57 (app t, *J* = 8.0 Hz, 1H), 3.41-3.36 (m, 1H), 3.26 (ddd, *J* = 8.9, 5.3, 3.3 Hz, 1H), 3.04-2.98 (m, 2H), 2.66 (s, 1H), 2.35 (app dt, *J* = 11.5, 4.0 Hz, 1H), 2.06-2.00 (m, 2H), 1.96 (app dt, *J* = 15.0, 3.6 Hz, 1H), 1.76-1.69 (m, 2H), 1.51 (app q, *J* = 11.3 Hz, 1H), 1.46-1.40 (m, 4H), 1.38 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 79.9, 78.4, 77.4, 72.5, 69.7, 68.8, 68.1, 38.3, 35.6, 29.5, 27.1, 26.0, 25.7.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_5$ $(M+Na)^+$: 295.1516, found 295.1522.



18 (characterization of major diastereomer only)

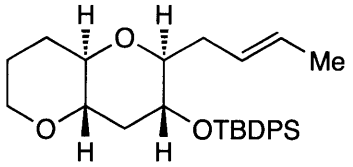
$[\alpha]^{22}_D$ = -11.9 (*c* = 0.20, $CDCl_3$).

IR (thin film, NaCl) 3440, 2939, 2869, 1453, 1369, 1222, 1041 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.36 (dddd, J = 7.4, 7.4, 6.4, 5.0 Hz, 1H), 4.11 (dd, J = 8.2, 6.0 Hz, 1H), 4.06 (ddd, J = 9.2, 6.2, 5.1 Hz, 1H), 4.03-3.95 (m, 2H), 3.61 (app t, J = 7.8 Hz, 1H), 3.50-3.44 (m, 1H), 3.32-3.21 (m, 2H), 2.50 (d, J = 4.1 Hz, 1H), 2.24-2.15 (m, 2H), 1.97 (app q, J = 10.8 Hz, 1H), 1.78 (ddd, J = 14.2, 7.5, 2.9 Hz, 1H), 1.74-1.60 (m, 3H), 1.50 (app qd, J = 11.3, 4.7 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 109.1, 81.5, 79.6, 78.7, 73.8, 71.1, 69.8, 69.0, 35.7, 30.8, 29.9, 27.1, 25.9, 24.7.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{24}O_5$ $(M+Na)^+$: 295.1516, found 295.1518.



20

Alkene 20: To a solution of alcohol **17** (380 mg, 1.39 mmol) in DMF (1 mL) was added imidazole (380 mg, 5.58 mmol) followed by *tert*-butyldiphenylchlorosilane (TBDPSCl, 714 μL, 767 mg, 2.79 mmol). The reaction was warmed to 50° for 17 h., then cooled and filtered through a short pad of SiO_2 (10% to 15% EtOAc in hexanes) to yield the desired silyl ether (R_f = 0.55 (20% EtOAc in hexanes)) as a mixture with TBDPSOH (R_f = 0.69 (20% EtOAc in hexanes)), a colorless oil (678 mg). This crude product was carried forward into the acetonide cleavage without further purification.

The crude silyl ether was dissolved in THF (5.1 mL), and deionized H_2O (1.3 mL) was added. Trifluoroacetic acid (568 μL, 876 mg, 7.68 mmol) was added slowly, resulting in smoking. The reaction was warmed to 35° for 24 h., then cooled to room temperature and quenched with NH_4OH (~2 mL, ~1.8 g, ~50 mmol). The solution was concentrated *in vacuo* (40°, 2 torr) to provide the crude diol (R_f = 0.11 (30% EtOAc/hexanes) or 0.40 (50% EtOAc in hexanes)) as a viscous colorless oil that crystallized upon standing. This crude was carried forward into periodate oxidation without further purification.

The crude diol was dissolved in a 1:1 mixture of THF:H_2O (6.4 mL) and cooled to 0° C, at which point $NaIO_4$ (821 mg, 3.84 mmol) was added. The mixture was stirred vigorously for 2 h., then diluted with H_2O (~25 mL) and extracted four times with Et_2O (50mL each). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the aldehyde (R_f = 0.65 (30% EtOAc in hexanes)). This crude aldehyde, which appeared nearly pure by ^{1}H NMR, was used without further purification. For prolonged storage of this aldehyde, it is recommended that the compound be frozen in benzene.

To a solution of this crude aldehyde in dry THF (7 mL) was added 1,1-diiodoethane (1.08 g, 3.84 mmol). A dry flask was charged with $CrCl_2$ (1.89 g, 15.4 mmol) to which was added dry THF (25 mL) to give a pale green slurry. The aldehyde and 1,1-diiodoethane solution were added dropwise by syringe to the $CrCl_2$ slurry over 5 min., at which point the reaction flask was covered with aluminum foil (to protect it from light) and stirred at rt for 20 h. The brown reaction solution was then quenched by pouring into a mixture of hexane (~50 mL) and H_2O (~50 mL). The aqueous layer was separated and extracted three times with Et_2O (50 mL each). The combined organics were washed twice with brine (15 mL each), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude alkene **20** as a yellow oil. The product was purified by column chromatography using a gradient of solvents (5% to 40% EtOAc in hexanes) to provide **20** as a pale yellow oil (495 mg, 1.10 mmol, 86% over 3 steps, *E*:*Z* = 8:1, R_f = 0.58 (10% EtOAc in hexanes)).

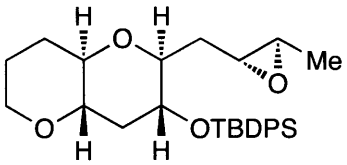
$[\alpha]^{22}_D$ = -29.5 (*c* = 0.81, $CDCl_3$)

IR (thin film, NaCl) 3071, 2933, 2856, 1590, 1473, 1463, 1451, 1428, 1361, 1281, 1100, 1081 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.72-7.64 (m, 4H), 7.46-7.34 (m, 6H), 5.53-5.38 (m, 2H), 3.84-3.78 (m, 1H), 3.42 (ddd, *J* = 10.9, 9.0, 4.6 Hz, 1H), 3.30-3.22 (m, 2H), 2.96 (ddd, *J* = 11.2, 8.9, 4.4 Hz, 1H), 2.70 (ddd, *J* = 11.6, 8.9, 4.2 Hz, 1H), 2.63-2.56 (m, 1H), 2.09 (app dt, *J* = 11.5, 4.4 Hz, 1H), 2.05-1.96 (m, 2H), 1.70-1.61 (m, 5H), 1.54 (app q, *J* = 11.4 Hz, 1H), 1.32 (app dq, *J* = 11.6, 5.5 Hz, 1H), 1.06 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 136.1, 134.3, 133.5, 130.0, 129.8, 127.9, 127.7, 127.7, 82.7, 77.7, 76.9, 71.1, 67.9, 39.7, 34.9, 29.4, 27.2, 25.6, 19.5, 18.3.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_3Si$ $(M+Na)^+$: 473.2482, found 473.2498.



21

Epoxide 21: To a solution of alkene **20** (100 mg, 0.22 mmol) in 2:1 v/v DMM:MeCN (7.5 mL) was added a 0.05 M aqueous solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M Na_2EDTA (5.0 mL), nBu_4HSO_4 (23 mg, 0.066 mmol), and chiral ketone **19** (57 mg, 0.22 mmol). The biphasic mixture was stirred vigorously at 0° C. To this mixture was added, simultaneously over 35 min. via syringe pump, a solution of Oxone (682 mg, 1.11 mmol) in 4 x 10^{-4} Na_2EDTA (2.5 mL) and a 0.89 M solution of K_2CO_3 (2.5 mL, 2.2 mmol).

After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 20 min at 0° C, at which point it was diluted with water (~10 mL). The aqueous layer was extracted four times with EtOAc (40 mL each), and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude epoxide **21** was purified by column chromatography using a gradient of solvents (5% to 40% EtOAc in hexanes) to provide **21**, a colorless oil, as an inseparable mixture of diastereomers (98 mg of a 5:1 mixture of epoxide diastereomers, 0.21 mmol combined, 95%), R_f = 0.60 (20% EtOAc in hexanes). Epoxide **21** could be further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.5% *i*PrOH in hexanes, 20 mL/min.; t_R of major diastereomer = 8.1 min.) to afford **21** in a d.r. of 20:1, which was characterized.

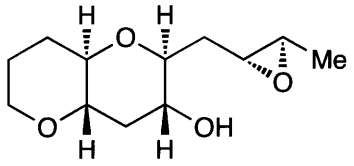
$[\alpha]^{22}_D$ = -30.7 (*c* = 1.29, $CDCl_3$).

IR (thin film, NaCl) 3072, 2931, 2857, 1739, 1590, 1473, 1428, 1361, 1281, 1098, 1032 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.70-7.64 (m, 4H), 7.46-7.35 (m, 6H), 3.84-3.79 (m, 1H), 3.46 (ddd, *J* = 10.7, 9.0, 4.6 Hz, 1H), 3.37 (app td, *J* = 8.8, 2.5 Hz, 1H), 3.28-3.22 (m, 1H), 2.98 (ddd, *J* = 11.2, 9.0, 4.4 Hz, 1H), 2.80-2.68 (m, 3H), 2.09 (app dt, *J* = 11.5, 4.4 Hz, 1H), 2.04-1.97 (m, 2H), 1.72-1.60 (m, 3H), 1.53 (app q, *J* = 11.2, 1H), 1.36-1.25 (m, 4H), 1.03 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 136.1, 134.1, 133.3, 130.1, 129.9, 127.9, 127.7, 80.4, 77.7, 76.7, 71.4, 67.9, 57.4, 54.2, 39.7, 34.3, 29.4, 27.2, 27.2, 25.6, 19.5, 17.9.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_4Si$ $(M+Na)^+$: 489.2437, found 489.2430.



10

Epoxy alcohol 10: To a solution of silyl ether **21** (6.9 mg, 0.015 mmol) in dry THF (300 μL) was added TBAF (1M in THF, 37 μL, 0.037 mmol). The reaction was warmed to 35 °C for 1.25 h, then cooled to room temperature and applied directly to a column of SiO_2. The silica was packed with 25% EtOAc in hexanes to which 2% Et_3N had been added, and the column run with a gradient of solvents from 25% to 100% EtOAc in hexanes, providing free alcohol **10** as a colorless oil (3.3 mg, 0.0145 mmol, 97%): R_f = 0.51 (100% EtOAc). Epoxy alcohol **10** cyclizes slowly if stored at room temperature as a neat oil. It is therefore best stored as a frozen benzene solution.

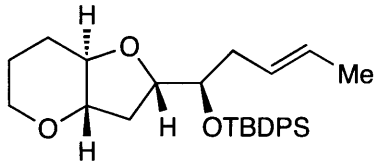
$[\alpha]^{22}_D = +15.1$ ($c = 0.045$, $CDCl_3$).

IR (thin film, NaCl) 3407, 2923, 2850, 1454, 1095 cm^{-1}.

^1H NMR (500 MHz, C_6D_6) δ 3.70-3.65 (m, 1H), 3.64-3.57 (m, 1H), 3.21 (ddd, J = 9.1, 5.4, 3.5 Hz, 1H), 3.02 (app td, J = 11.9, 2.3 Hz, 1H), 2.91-2.85 (m, 2H), 2.82 (ddd, J = 11.3, 8.9, 4.2 Hz, 1H), 2.46-2.39 (m, 2H), 2.18 (s, 1H), 2.03 (app dt, J = 14.8, 3.5 Hz, 1H), 1.92-1.87 (m, 1H), 1.69-1.59 (m, 2H), 1.42 (app qt, J = 13.0, 4.2 Hz, 1H), 1.33-1.25 (m, 1H), 1.17 (app dd, J = 13.4, 2.0 Hz, 1H), 0.98 (d, J = 5.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 80.3, 78.3, 77.3, 69.0, 68.1, 56.7, 54.6, 38.5, 34.4, 29.5, 25.7, 17.7.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+Na)^+$: 251.1254, found 251.1263.



22

Alkene 22: To a solution of alcohol **18** (350 mg, 1.29 mmol) in DMF (3 mL) was added first imidazole (440 mg, 6.46 mmol) and then TBDPSCl (860 μL, 920 mg, 3.36 mmol). The reaction was warmed to 50 °C for 36 h., then cooled and applied directly to a column of SiO_2. Purification with a gradient of solvents (10% to 20% EtOAc in hexanes) yielded the desired silyl ether (R_f = 0.29 (20% EtOAc in hexanes), 404 mg, 0.79 mmol, 61%) as a colorless oil that solidified upon storage at -20 °C.

This acetonide (360 mg, 0.70 mmol) was dissolved in THF (2.8 mL), and deionized H_2O (0.7 mL) was added. Trifluoroacetic acid (261 μL, 402 mg, 3.52 mmol) was added slowly, resulting in smoking. The reaction was warmed to 35 °C for 19 h., then cooled to rt and quenched with NH_4OH (~1 mL, ~0.9 g, ~25 mmol). The reaction solution was concentrated *in vacuo* (40 °C, 2 torr) to provide the crude diol (R_f = 0.50 (100% EtOAc)) as a viscous, colorless oil. The crude product was carried forward into periodate oxidation without further purification.

The crude diol was dissolved in a 1:1 mixture of THF:H_2O (3.5 mL) and cooled to 0 °C, at which point $NaIO_4$ (452 mg, 2.1 mmol) was added. The mixture was stirred vigorously for 2 h, then warmed to room temperature and stirred for an additional hour. The reaction was then diluted with H_2O (~25 mL) and extracted three times with Et_2O (40mL each). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude aldehyde (R_f = 0.65 (30% EtOAc in hexanes))

as a golden brown oil. The crude aldehyde was used without further purification. For prolonged storage of this crude aldehyde, it is recommended that the compound be frozen in benzene.

To a solution of this crude aldehyde in dry THF (7.6 mL) was added 1,1-diiodoethane (596 mg, 2.12 mmol). A dry flask was charged with $CrCl_2$ (1.04 g, 8.46 mmol), to which was added dry THF (10 mL) to give a pale green slurry. The aldehyde and 1,1-diiodoethane solution was added dropwise to the $CrCl_2$ slurry over 5 min., at which point the reaction flask was covered with aluminum foil (to protect it from light) and stirred at room temperature for 20 h. The brown reaction solution was then quenched by pouring into a mixture of hexane (~50 mL) and H_2O (~50 mL). The aqueous layer was extracted three times with Et_2O (50 mL each). The combined organics were washed twice with brine (15 mL each), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude alkene **22** as a yellow oil. The product was purified by column chromatography using a gradient of solvents (5% to 40% EtOAc in hexanes) to provide **22** as a pale yellow oil (290 mg, 0.64 mmol, 91% over 3 steps, *E*:*Z* = 9:1, R_f = 0.67 (20% EtOAc in hexanes)).

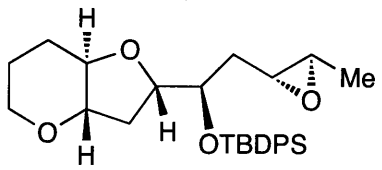
$[\alpha]^{22}_D$ = -22.7 (*c* = 0.68, CH_2Cl_2)

IR (thin film, NaCl) 3071, 3049, 2932, 2856, 1589, 1473, 1427, 1127, 1112, 1086, 1070 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.79-7.69 (m, 4H), 7.45-7.35 (m, 6H), 5.17 (app dq, *J* = 15.2, 6.2 Hz, 1H), 5.07 (app dtd, *J* = 15.2, 7.1, 1.3 Hz, 1H), 4.10 (ddd, *J* = 9.5, 6.5, 3.4 Hz, 1H), 4.05 (ddd, *J* = 8.3, 4.9, 3.5 Hz, 1H), 3.99 (app dd, *J* = 11.5, 4.8 Hz, 1H), 3.46 (app td, *J* = 12.0, 2.8 Hz, 1H), 3.39 (ddd, *J* = 11.2, 8.9, 3.9 Hz, 1H), 3.21 (ddd, *J* = 11.1, 9.0, 6.6 Hz, 1H), 2.21-2.06 (m, 3H), 2.01-1.89 (m, 2H), 1.71-1.65 (m, 1H), 1.65-1.54 (m, 1H), 1.49 (dd, *J* = 6.2, 1.1 Hz, 3H), 1.46 (app qd, *J* = 11.8, 4.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 136.2, 134.9, 134.0, 129.8, 127.9, 127.7, 127.7, 126.4, 81.6, 78.8, 78.2, 75.4, 69.0, 37.6, 29.8, 29.7, 27.3, 24.8, 19.7, 18.1.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_3Si$ $(M+Na)^+$: 473.2482, found 473,2495.



23

Epoxide 23: To a solution of alkene **22** (120 mg, 0.27 mmol) in DMM:MeCN (2:1 v/v,

9.0 mL) was added a 0.05 M aqueous solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M Na_2EDTA (6.0 mL), nBu$_4HSO_4$ (27 mg, 0.080 mmol), and chiral ketone **19** (69 mg, 0.27 mmol). The biphasic mixture was stirred vigorously at 0 °C, and Oxone (818 mg, 1.33 mmol) dissolved in a 4 x 10^{-4} M Na_2EDTA aqueous solution (3.0 mL) was simultaneously added with an aqueous solution of K_2CO_3 (0.89 M, 3.0 mL, 2.67 mmol) over 30 min. via syringe pump. The resulting mixture was stirred an additional 20 min. at 0 °C, at which point it was diluted with water (~10 mL). The aqueous layer was separated and extracted three times with Et_2O (40 mL each), and the combined organics were washed with brine (~10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude epoxide **23** was purified by column chromatography using a gradient of solvents (5% to 60% EtOAc in hexanes) to provide a small amount of unreacted alkene **22** (10 mg, 0.022 mmol, 8%) and the desired epoxide **23**, a colorless oil, as an inseparable mixture of diastereomers (89 mg of an approximately 6:1 mixture of epoxide diastereomers, 0.19 mmol combined, 72%), R_f = 0.21 in 20% EtOAc in hexanes and R_f = 0.38 in 30% EtOAc in hexanes. Epoxide **23** could be further purified via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 3.0% *i*PrOH in hexanes, 20 mL/min.; t_R of major diastereomer = 5.7 min.., with the highest purity material collected on the trailing edge (i.e., the right side) of this peak) to afford **23** in a d.r. of 20:1, which was characterized:

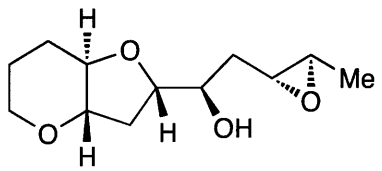
$[\alpha]^{22}_D$ = -20.3 (*c* = 0.34, $CDCl_3$).

IR (thin film, NaCl) 2933, 2857, 1751, 1428, 1383, 1112, 1076 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79-7.75 (m, 2H), 7.72-7.69 (m, 2H), 7.46-7.42 (m, 2H), 7.42-7.37 (m, 4H), 4.19 (ddd, *J* = 9.2, 6.5, 3.8 Hz, 1H), 4.14 (app quint, *J* = 4.1 Hz, 1H), 4.00-3.96 (m, 1H), 3.46 (app td, *J* = 12.0, 2.6 Hz, 1H), 3.35 (ddd, *J* = 11.2, 9.0, 3.9 Hz, 1H), 3.21 (ddd, *J* = 11.0, 8.9, 6.6 Hz, 1H), 2.41-2.37 (m, 2H), 2.17-2.11 (m, 2H), 2.06 (app td, *J* = 11.0, 9.2 Hz, 1H), 1.71-1.65 (m, 1H), 1.64-1.53 (m, 2H), 1.53-1.43 (m, 2H), 1.11 (d, *J* = 4.9 Hz, 3H), 1.09 (s, 9H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 136.1, 134.5, 133.6, 129.9, 127.8, 127.8, 81.5, 79.4, 78.4, 74.1, 69.0, 56.3, 54.7, 37.1, 30.5, 29.8, 27.2, 24.8, 19.7, 17.6.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_4Si$ $(M+Na)^+$: 489.2432, found 489.2445.



7

Epoxy alcohol 7: To a solution of silyl ether **23** (22 mg, 0.047 mmol, 20:1 dr) in dry

THF (300 μL) was added TBAF (1M in THF, 118 μL, 0.118 mmol). The reaction was warmed to 40 °C for 6 h., then cooled to room temperature and applied directly to a pad of SiO_2. The silica was packed in 25% EtOAc in hexanes to which 2% Et_3N had been added, and the column run with a gradient of solvents from 25% to 100% EtOAc in hexanes, providing free alcohol **7** (R_f = 0.44 (100% EtOAc), 9.4 mg, 0.047 mmol, 88%) as a colorless oil which solidified upon storage at 4 °C. Spectral data and other characterization were consistent with that already reported by our group.[2a] However, as that earlier report describes epoxy alcohol **7** in relatively low diastereopurity, we collected characterization data for a sample of **7** in 20:1 d.r. and report it here:

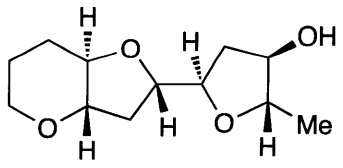
$[\alpha]^{22}_D$ = +18.8 (*c* = 0.47, CH_2Cl_2)

IR (thin film, NaCl) 3406, 2975, 2945, 2902, 2851, 1451, 1307, 1275, 1152, 1123, 1086, 1072, 1041 cm^{-1}.

^1H NMR (500 MHz, C_6D_6) δ 3.93-3.86 (m, 2H), 3.77-3.72 (m, 1H), 3.25 (ddd, *J* = 10.8, 8.9, 3.9 Hz, 1H), 3.10 (app td, *J* = 11.9, 2.8 Hz, 1H), 3.02 (ddd, *J* = 10.8, 8.9, 6.9 Hz, 1H), 2.67 (ddd, *J* = 6.9, 3.6, 2.2 Hz, 1H), 2.51 (qd, *J* = 5.2, 2.2 Hz, 1H), 2.43 (s, 1H), 2.11-1.97 (m, 3H), 1.63 (ddd, *J* = 14.2, 8.9, 3.7 Hz, 1H), 1.39 (ddd, *J* = 14.2, 7.1, 3.1 Hz, 1H), 1.35-1.26 (m, 2H), 1.18-1.10 (m, 1H), 1.00 (d, *J* = 5.2 Hz, 3H);

^{13}C NMR (100 MHz, C_6D_6) δ 82.3, 80.1, 79.1, 71.9, 68.9, 57.2, 54.5, 35.5, 31.5, 30.6, 25.2, 17.9.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+Na)^+$: 251.1254, found 251.1258.



8

THF side product 8: A solution of epoxy alcohol **7** (3.0 mg, 0.015 mmol) in CH_2Cl_2 (2 mL) was transferred into a 5 mL microwave reaction vial, along with a magnetic stir bar. To this was added silica gel (300 mg) that had been dried in the oven overnight and then cooled in a dessicator. The tube was capped and the mixture heated by microwave irradiation to 90 °C for 3 h. After cooling to room temperature, the slurry was filtered through a glass frit, and the silica gel was washed repeatedly with ~10 mL of a 10% solution of MeOH in EtOAc. The organic solution was concentrated *in vacuo* and purified by column chromatography (100% EtOAc) to afford **8** (1.5 mg, 0.0075 mmol, 50%) as a colorless oil (R_f = 0.28 (100% EtOAc)).

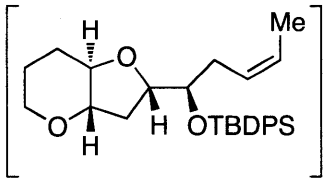
$[\alpha]^{22}_D$ = -17.5 (*c* = 0.075, CH_2Cl_2)

IR (thin film, NaCl) 3418, 2924, 2853, 1726, 1461, 1378, 1277, 1125, 1066, 1013 cm^{-1}.

^1H NMR (500 MHz, D_2O) δ 4.26 (m, 2H), 4.07-4.00 (m, 2H), 3.94 (app quintet, J = 6.1 Hz, 1H), 3.56 (app td, J = 12.2, 2.6 Hz, 1H), 3.42-3.34 (m, 2H), 2.46 (app dt, J = 13.0, 6.6 Hz, 1H), 2.36 (app td, J = 11.2, 5.8 Hz, 1H), 2.21-2.15 (m, 1H), 1.83-1.71 (m, 3H), 1.64 (app qt, J = 13.1, 4.5 Hz, 1H), 1.53 (app qd, J = 11.4, 4.5 Hz, 1H), 1.21 (d, J = 6.3 Hz, 3H).

^{13}C NMR (125 MHz, D_2O) δ 81.6, 80.6, 79.4, 79.3, 79.0, 76.6, 69.5, 35.5, 31.6, 29.1, 24.4, 17.9.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+Na)^+$: 251.1254, found 251.1263.

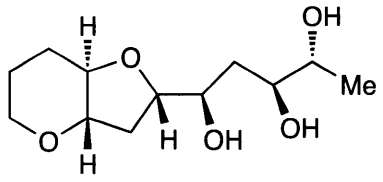


24

***cis*-Alkene 24:** A solution of *trans*-alkene **22** (54 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (2.4 mL) and cooled to -78 °C. Ozone was bubbled through the reaction mixture until a blue color remained, about 5 min. Pure oxygen gas was then bubbled through the reaction mixture for 2 min., followed by argon for 2 min. Triphenyl phosphine (47 mg, 0.18 mmol) was added to the reaction, and the solution was allowed to warm gradually to room temperature over approximately 15 min. The solution was then concentrated to provide the crude aldehyde (R_f = 0.32 (20% EtOAc in hexanes)) as a yellow-brown oil, which was filtered through a short plug of silica (5% to 40% EtOAc in hexanes) to remove unreacted PPh_3. The resulting crude aldehyde was used without further purification.

The *Z*-selective Wittig olefination was carried out according to the procedure of Denmark and coworkers. A dry flask was charged with KHMDS (26 mg, 0.13 mmol) and ethyltriphenylphosphonium bromide (Ph_3PEtBr) (52 mg, 0.14 mmol). To this was added THF (200 μL) and freshly distilled hexamethylphosphoramide (HMPA, 50 μL), and the mixture was stirred at room temperature for 30 min. to provide a clear orange-yellow solution. In a second flask, the crude aldehyde from the preceding step was dissolved in THF (150 μL). Upon cooling the newly-formed phosphorane solution to -78 °C, the aldehyde solution was slowly added dropwise over approximately 3 min. The flask containing the aldehyde was washed out with a further 100 μL, and this was added dropwise to the phosphorane solution. The yellow solution was allowed to warm gradually to room temperature over 5 h, at which point it was quenched with water (5 mL), diluted with Et_2O, extracted three times with Et_2O, washed with brine, dried over

$MgSO_4$, and concentrated *in vacuo* to provide the crude alkene **24** in >20:1 *Z*:*E* by ^1H NMR. Crude **24** was carried forward into dihydroxylation without further purification.



9a

Triol 9a: One half of the crude *cis*-alkene **24** prepared in the previous step was dissolved in THF (100 μL). In a separate vial, AD mix α (70 mg) was dissolved in a mixture of *t*BuOH (250 μL) and H_2O (250 μL). This solution was cooled to 4 °C and stirred 15 min. The solution of crude **24** was then added, and the resulting orange solution stirred vigorously at 4 °C for 18 h, at which point it was diluted with H_2O and Et_2O. The aqueous layer was extracted three times with Et_2O, and the combined organics were concentrated *in vacuo* without drying to provide the crude diol (R_f = 0.54 (100% EtOAc)). ^1H NMR analysis at this point indicated a 67:33 mixture of diastereomers, with the configuration of the major diastereomer assumed, based on Sharpless's rules for induction in asymmetric dihydroxylation. This crude mixture was carried into desilylation without further purification.

To a solution this crude silyl ether in THF (300 μL) was added TBAF (1 M in THF, 13 μL, 0.013 mmol). The reaction solution was stirred at room temperature for 16 h., then applied directly to a pad of SiO_2. The column was run with a gradient of solvents from 5% to 15% MeOH in EtOAc, providing cleanly triol **9a** as the major product (0.8 mg, 0.0032 mmol, 6% over 4 steps, R_f = 0.24 (10% MeOH in EtOAc)) as well as some of the diastereomeric triol **9b** (R_f = 0.32 (10% MeOH in EtOAc)).

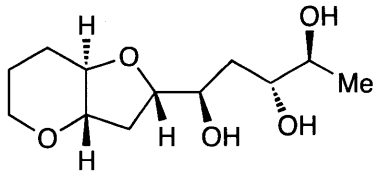
$[\alpha]^{22}_D$ = +2.2 (*c* = 0.040, EtOAc)

IR (thin film, NaCl) 3377, 2924, 2855, 1996, 1642, 1379, 1123, 1061 cm^{-1}.

^1H NMR (500 MHz, D_2O) δ 4.08 (ddd, *J* = 9.3, 6.6, 4.4 Hz, 1H), 4.01-3.94 (m, 2H), 3.76-3.70 (m, 2H), 3.52 (app td, *J* = 12.2, 2.5 Hz, 1H), 3.39-3.30 (m, 2H), 2.23 (app dt, *J* = 11.2, 6.3 Hz, 1H), 2.18-2.12 (m, 1H), 1.87-1.72 (m, 2H), 1.60 (app qt, *J* = 13.0, 4.6 Hz, 1H), 1.54-1.41 (m, 3H), 1.11 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (125 MHz, D_2O) δ 80.9, 80.7, 78.9, 71.6, 71.3, 70.1, 69.5, 34.7, 30.0, 29.1, 24.4, 17.0.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{22}O_5$ $(M+Na)^+$: 269.1359, found 269.1364.



9b

Triol 9b: One half of the crude *cis*-alkene **24** prepared in the procedure above was dissolved in THF (100 μL). In a separate vial, AD mix β (70 mg) was dissolved in a mixture of *t*BuOH (250 μL) and H_2O (250 μL). This solution was cooled to 4 °C and stirred 15 min. The solution of crude **24** was then added, and the resulting orange solution stirred vigorously at 4 °C for 18 h, at which point it was diluted with H_2O and Et_2O. The aqueous layer was extracted three times with Et_2O, and the combined organics were concentrated *in vacuo* without drying to provide the crude diol (R_f = 0.54 (100% EtOAc)). ^{1}H NMR analysis at this point indicated a 55:45 mixture of diastereomers, with the configuration of the major diastereomer assumed, based on Sharpless's rules for induction in asymmetric dihydroxylation. This crude mixture was carried into desilylation without further purification.

To a solution this crude silyl ether in THF (300 μL) was added TBAF (1 M in THF, 13 μL, 0.013 mmol). The reaction solution was stirred at room temperature for 16 h., then applied directly to a pad of SiO_2. The column was run with a gradient of solvents from 5% to 15% MeOH in EtOAc, providing cleanly triol **9b** as the major product (0.9 mg, 0.0037 mmol, 6% over 4 steps, R_f = 0.32 (10% MeOH in EtOAc)) as well as some of the diastereomeric triol **9a** (R_f = 0.24 (10% MeOH in EtOAc)).

$[\alpha]^{22}_D$ = -13.2 (*c* = 0.040, EtOAc)

IR (thin film, NaCl) 3377, 2924, 2855, 1996, 1604, 1378, 1123, 1063 cm^{-1}.

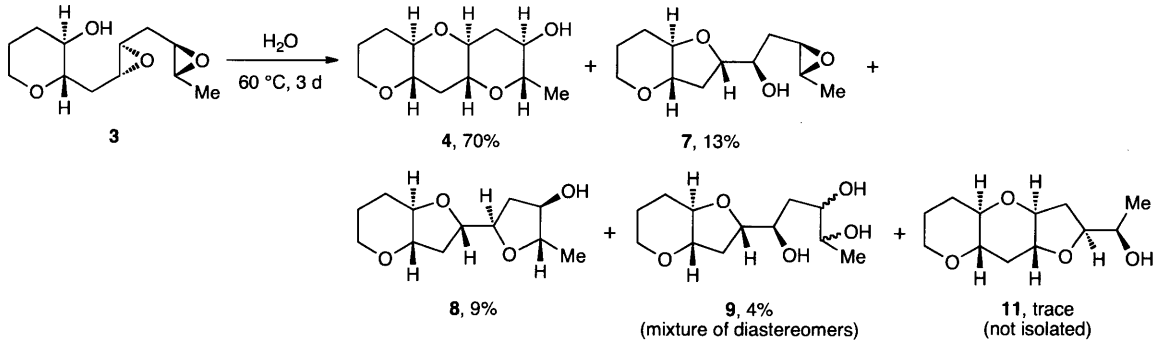
^{1}H NMR (500 MHz, D_2O) δ 4.12 (ddd, *J* = 9.3, 6.5, 4.5 Hz, 1H), 4.01-3.94 (m, 2H), 3.77-3.67 (m, 2H), 3.52 (app td, *J* = 12.1, 2.5 Hz, 1H), 3.39-3.29 (m, 2H), 2.23 (app dt, *J* = 11.2, 6.3 Hz, 1H), 2.17-2.11 (m, 1H), 1.84 (app q, *J* = 10.3 Hz, 1H), 1.79-1.70 (m, 2H), 1.60 (app qt, *J* = 13.1, 4.6 Hz, 1H), 1.54-1.44 (m, 2H), 1.11 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (125 MHz, D_2O) δ 80.9, 80.0, 78.9, 73.7, 71.8, 70.6, 69.5, 35.2, 29.8, 29.1, 24.4, 17.0.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{22}O_5$ $(M+Na)^+$: 269.1359, found 269.1369.

Experimental Procedures for Cyclizations and Cascade Reactions in Batch:

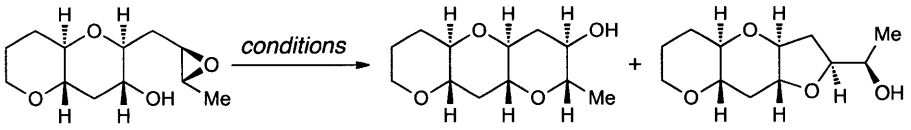
Cascade reaction of THP-templated diepoxy alcohol **3** promoted by neutral water:



Diepoxy alcohol **3** (20:1 d.r., 24.7 mg, 0.108 mmol) was dissolved in deionized water (5.4 mL) in a 20 mL vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was heated to 60 °C under air for 3 d. The solution was then cooled to room temperature and concentrated *in vacuo* (2 torr, 40 °C). The crude product mixture was purified by column chromatography using a gradient of solvents (50% EtOAc in hexanes to 100% EtOAc in 10% MeOH in EtOAc) to separate THP triad **4** (17.2 mg, 0.075 mmol, 70%, R_f = 0.51 (EtOAc)), a white crystalline solid, from 6,5-fused epoxy alcohol **7** (3.3 mg, 13%, R_f = 0.44 (EtOAc)), THF side product **8** (2.1 mg, 0.009 mmol, 9%, R_f = 0.28 (EtOAc)), and two diastereomeric hydrolysis products **9a** and **9b** (1.0 mg of an approximately 2:1 mixture of **9a**:**9b**, 0.004 mmol, 4%, R_f of **9a** = 0.24 (10% MeOH in EtOAc) and R_f of **9b** = 0.32 (10% MeOH in EtOAc)). The configurations of **9a** and **9b** could not be determined by NMR spectroscopy. However, we prepared **9a** and **9b** independently via asymmetric dihydroxylation (*vide supra*). Following Sharpless's rules of asymmetric induction in asymmetric dihydroxylation, we were able to assign the configurations of **9a** and **9b**.

The ratio of **4**:**11**:**8** in the crude cascade product mixture could be determined by gas chromatography (GC). To the crude mixture was added EtOAc, and the slurry of solid buffer residue was sonicated in an ultrasound bath. The organic solution was then filtered through a PTFE syringe filter. The sample was injected into an Agilent 7890A GC-FID equipped with an Agilent HP-5 column (30 m x 0.32 mm, 0.25 μm) using the following program: 2 mL/min. flow rate, initial T = 35 °C hold for 5 min., then heat 20 °C/min. to 250 °C, then hold 5 min. at 250 °C. t_R(**4**) = 14.08 min., t_R(**11**) = 14.16 min., t_R(8) = 14.19 min. From reactions in D_2O at pD 7.0 at 70 °C (0.1 M KP_i buffer, 2-4 d. reaction time), the ratio of **4**:**11** was found to be 15.6:1 (average of 3 experiments).

Cyclization reactions of THP diad-templated epoxy alcohol **10**:



10 *endo* (**4**) *exo* (**11**)

Conditions and results:

entry	promoter/ solvent	T (°C)	time	regioselectivity (**4**:**11**) [a]
1	Cs_2CO_3/MeOH [b]	rt	18 h	0.64:1
2	CSA/CH_2Cl_2 [c]	rt	18 h	1.4:1
3	BF_3•OEt_2/CH_2Cl_2 [d]	-78 to rt	30 min	1.5:1
4	H_2O [e]	rt	19 d	>20:1
5	D_2O [f] (pD 7, 0.1 M KP*i*)	70	24 h	20:1

[a] Regioselectivity determined by ^{1}H NMR spectroscopy. Results are the average of at least 2 experiments.
[b] Cs_2CO_3 (30 equiv), 0.02 M. [c] (±)-CSA (1 equiv), 0.02 M. [d] BF_3·OEt_2 (0.25 equiv), 0.02 M.
[e] Deionized water, 0.02 M. [f] D_2O buffered to pD 7.0 with 0.1 M K_2HPO_4/KH_2PO_4.

Reaction of 10 promoted by Cs_2CO_3/MeOH: To a sample of epoxy alcohol **10** (0.6 mg, 0.0024 mmol) in a 2 mL vial was added a 0.60 M aqueous solution of Cs_2CO_3 in MeOH (120 μL, 0.072 mmol, prepared by dissolving 235 mg Cs_2CO_3 to 1.2 mL volume in anhydrous methanol). The resulting clear, colorless solution was stirred under air at room temperature for 18 h, at which point it was quenched with the addition of sat. $NH_4Cl_{(aq)}$ (~200 μL). The reaction solution was concentrated *in vacuo* (40 °C, 2 torr) without drying to afford a solid residue. To the crude product mixture was added $CDCl_3$ (700 μL), and the resulting slurry was placed in an ultrasound bath for 5 min. The chloroform solution was then analyzed by ^{1}H NMR to determine **4**:**11**.

Reaction of 10 promoted by CSA in CH_2Cl_2: To a sample of epoxy alcohol **10** (0.6 mg, 0.0024 mmol) in a 2 mL vial was added CH_2Cl_2 (125 μL). To this was added (+/-)-CSA (0.6 mg, 0.0024 mmol), and the resulting clear, colorless solution was stirred under air at room temperature for 18 h. The reaction was then quenched with sat. $NaHCO_{3(aq)}$ (2 drops). The reaction solution was concentrated *in vacuo* (40 °C, 2 torr) without drying to afford a trace of residue, which was taken up into $CDCl_3$ (700 μL) and analyzed by ^{1}H NMR to determine **4**:**11**.

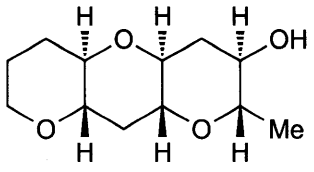
Reaction of 10 promoted by BF_3 in CH_2Cl_2: A solution of epoxy alcohol **10** (0.6 mg, 0.0024 mmol) in CH_2Cl_2 (110 μL) in a dried 5 mL round bottom flask was cooled to -78

°C. To this was added a 0.05 M solution of BF_3•OEt_2 (12 μL, 0.0006 mmol, prepared from the dissolution of 71 mg of BF_3•OEt_2 in 10 mL CH_2Cl_2), and the reaction was stirred at -78 °C for 30 min. The dry ice bath was removed, and the reaction was allowed to warm for 1 min., at which point it was quenched with sat. $NaHCO_{3(aq)}$ (2 drops). The reaction solution was concentrated *in vacuo* (40 °C, 2 torr) without drying to afford a trace of residue, which was taken up into $CDCl_3$ (700 μL) and analyzed by ^1H NMR to determine **4**:**11**.

Representative procedure for the reaction of 10 in aqueous media: Epoxy alcohol **10** (0.9 mg, 0.0040 mmol, >20:1 dr) was dissolved either in deionized water (200 μL) or 0.1 M solution of potassium phosphate buffer in deionized water (200 μL) and stirred at room temperature under air for 13-19 d. The reaction solutions were concentrated *in vacuo* (40 °C, 2 torr) without drying. The crude product mixture was analyzed by ^1H NMR to determine the ratio of **4:11**. For reactions of **10** in deionized water at room temperature, **4**:**11** was found to be 22:1 (average of 2 experiments).

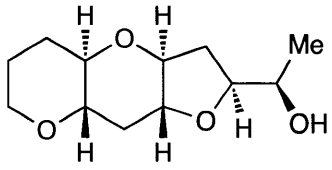
Dependence of Regioselectivity on pH in Reactions of **10**		
entry	pH (0.1 M KP_i buffer)	*endo*:*exo* selectivity (**4:11**)
1	2.0	2.6:1
2	2.0	3.1:1
3	3.0	2.8:1
4	4.0	6.2:1
5	4.0	5.0:1
6	5.0	13:1
7	6.0	20:1
8	6.0	28:1
9	7.0	28:1
10	7.0	24:1
11	8.0	15:1
12	8.0	17:1
13	9.0	6.3:1
14	10.0	3.2:1
15	10.0	2.9:1
16	11.0	1.1:1
17	12.0	1.0:1
18	12.0	1.0:1

Protocol for the separation of 4 and 11: The crude product mixture of **4** and **11** can be separated by column chromatography (load crude mixture as solution in CH_2Cl_2, pack column in 50% EtOAc in hexanes, run 50% EtOAc in hexanes) to afford analytically pure samples of **4** (R_f = 0.51 (100% EtOAc) and **11** (R_f = 0.42 (100% EtOAc)).



4

THP triad 4: This compound has already been characterized (see Chapter II).



11

6,6,5-fused triad 11: $R_f = 0.42$ (EtOAc)

$[\alpha]^{22}_D = -9.4$ ($c = 0.18$, CH_2Cl_2)

IR (thin film, NaCl) 3430, 2924, 2852, 1739, 1462, 1341, 1068, 1025 cm^{-1}.

^1H NMR (500 MHz, D_2O (referenced H_2O peak at 4.79 ppm) δ 4.15 (dddd, J = 10.5, 6.4, 4.6, 0.7 Hz, 1H), 3.99-3.90 (m, 2H), 3.59 (ddd, J = 10.7, 9.6, 6.5 Hz, 1H), 3.48-3.41 (m, 2H), 3.35 (ddd, J = 10.9, 9.4, 3.9 Hz, 1H), 3.22 (ddd, J = 11.4, 10.1, 4.5 Hz, 1H), 2.43 (app dt, J = 10.3, 4.1 Hz, 1H), 2.24 (dt, J = 11.1, 6.5 Hz, 1H), 2.11-2.04 (m, 1H), 1.86-1.65 (m, 3H), 1.56-1.46 (m, 2H), 1.12 (dd, J = 6.5, 0.7 Hz, 3H).

^{13}C NMR (125 MHz, D_2O (referenced to MeOH (1 μL) added to sample, at 49.50 ppm) δ 82.8, 80.9, 79.7, 69.6, 69.0, 35.0, 29.3, 29.1, 25.3, 17.8.

`HR-MS (DART) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+H)^+$: 229.1434, found 229.1425.

Kinetic Procedures, Data, and Analysis

General experimental considerations. Kinetic measurements were made using ^{1}H NMR spectroscopy on a Varian Inova 500 MHz spectrometer equipped with an inverse broadband gradient probe (gHX) thermostated at 70 °C. The temperature of the spectrometer was calibrated using an ethylene glycol external standard. Unless otherwise stated, kinetic data was obtained in triplicate to three half lives in deuterated 0.1 M potassium phosphate buffer (pD 7.0). The rate constants determined from regression analysis or from computer simulation are reported in Scheme 2 and Tables S1-S3 as an average of the three experiments with the average error reported in parenthesis. Buffers were prepared at room temperature, and their pD was adjusted to 7.0 using 0.1 M solutions of K_2DPO_4 or KD_2PO_4 at the reaction temperature using a Symphony™ Posi-pHlo Ag/AgCl pH glass electrode. The pH electrode was calibrated at the reaction temperature with standard pH solutions. A correction factor was applied to all measurement to account for the solvent isotope effect inherent to the glass electrode (pD = measured pH + 0.4).[25] All chemical shifts are reported in ppm and are referenced against the HDO peak (4.310 ppm at 70 °C).[23]

General experimental procedure. The substrate (0.7-1.5 mg) was dissolved in pD 7.0 buffer (0.7 mL) containing a small amount of DMSO (2.0 μL, 2.2 mg, 28 μmol) as an internal standard. The mixture was stirred briefly, then filtered through a PTFE syringe filter into a J. Young tube. The J. Young tube was filled from the bottom, taking care not to scratch the tube. Samples in scratched tubes appear prone to undergoing degassing upon heating, which is severely detrimental to the NMR signal. To further prevent degassing, the J. Young tube was pressurized with argon (2-5 atm). The NMR tube was injected into the thermostated spectrometer and allowed to warm to 70 °C. After three minutes, the spectrometer was shimmed and kinetic data was obtained using the array function on the pre acquisition delay parameter (Varian). The concentrations of all species were determined by integration of the methyl resonances relative to the DMSO standard. The overlapping resonances for cyclizations of **3** were deconvoluted as described in the text. All measurements were made in triplicate using substrates in at least 20:1 d.r. (*vide supra*). The rate constants reported in Scheme 2 and Tables S1-S3 are reported as average values from these experiments. Error is reported as average error in the measurement.

Determination of rate constants from concentration vs. time data. Determination of rate constants for cyclizations of independently prepared monoepoxides **7** and **10** was straightforward from concentration vs. time data (see Figure S1 for representative examples). The raw data were fit to a two-parameter exponential function ($f(t)=ae^{-kt}$) using the "General Fit" function in the Kaleidagraph™ v. 3.6 software (based on the Levenberg-Marquardt algorithm[26]). Elementary rate constants were determined from the

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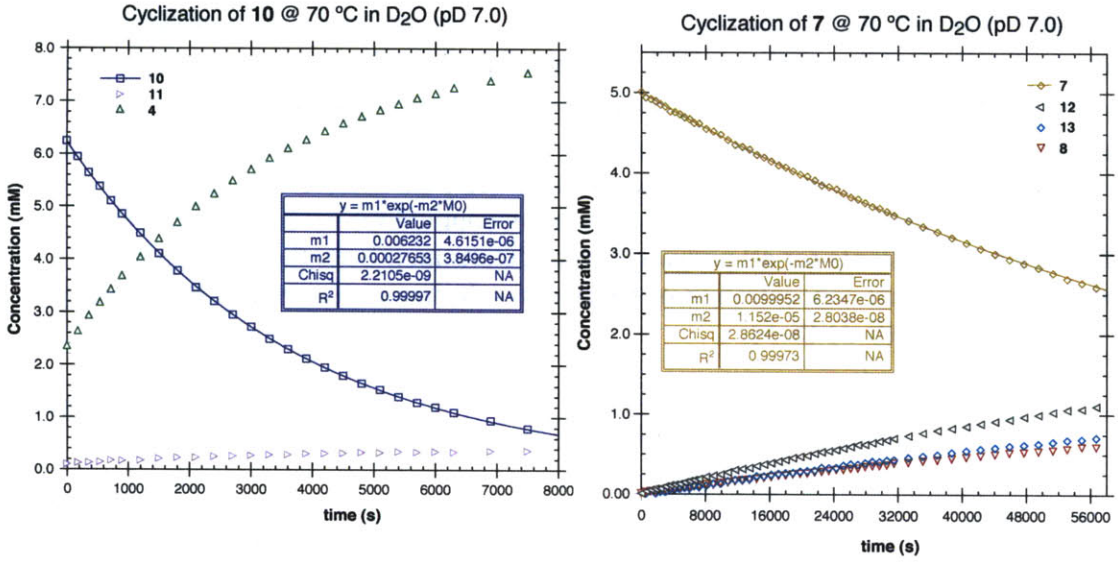
[25] Cook, P. A.; Clelan, W. W. *Enzyme Kinetics and Mechanism*, Garland Science; New York, 2007.

[26] (a) Levenberg, K. *Quart. Appl. Math.* **1944**, *2*, 164-168. (b) Marquardt, D. *SIAM J. Appl. Math.* **1963**, *11*, 431-441. (c) Bates, D. M.; Watts, D. G. *Nonlinear Regression and Its Applications*. New York: Wiley, 1988.

observed rate constant and the selectivity of the reaction determined at the end of the reaction by NMR. Due to the very slow reaction of **7**, data was only collected for the first half-life and was repeated only once. These data appear in the text and in Table S3 for comparison with rate constants determined from diepoxide **3** by simulation of the concentration vs. time data (*vide infra*).

Figure S1. *Representative concentration vs. time plots and first order fits for cyclizations of* ***10*** *(left) and 7 (right) in* D_2O *(pD 7.0) at 70 °C.*



Due to competing side reactions, determination of all rate constants for cyclizations of diepoxide **3** could not be achieved in a similar fashion as for the monoepoxides. However, most rate constants could be estimated from concentration vs. time data determined for species **3**, **4**, **10**, and **7** using the following procedure. The observed rate constant for the first step ($k_{obs}^{\mathbf{3}}$) could be obtained in a straightforward fashion by linear regression analysis from ln([**3**]) vs. time data. The second step kinetics was more complicated. The observed rate constant for the formation of **4** and **11** ($k_{obs}^{\mathbf{10}}$) could be determined either from concentration vs. time data of the intermediate (**10**) or the major product (**4**) using equations (S-1) or (S-2), which describe intermediate and product formation in a consecutive reaction mechanism, respectively[18]:

$$[\mathbf{10}]_t = \frac{[\mathbf{3}]_0 * k_{obs}^{\mathbf{3}}}{k_{obs}^{\mathbf{10}} - k_{obs}^{\mathbf{3}}}\left[e^{-k_{obs}^{\mathbf{3}} * t} - e^{-k_{obs}^{\mathbf{10}} * t}\right] \quad \text{(S-1)}$$

$$[\mathbf{4}]_t = [\mathbf{3}]_0 + \frac{[\mathbf{3}]_0}{k_{obs}^{\mathbf{3}} - k_{obs}^{\mathbf{10}}}\left[k_{obs}^{\mathbf{10}} * e^{-k_{obs}^{\mathbf{3}} * t} - k_{obs}^{\mathbf{3}} * e^{-k_{obs}^{\mathbf{10}} * t}\right] \quad \text{(S-2)}$$

Equations S-1 and S-2 are valid only when [**10**] and [**4**] are negligible at t = 0. However, this approximation is inaccurate in our case, as the cascade reaction had invariably proceeded to a significant extent by the time we could begin collecting kinetics data. To ensure sufficiently good shims for the long reaction times, data collection could not be initiated until 30-60 minutes after the sample reached the reaction temperature. Therefore, to use equations x and y, the actual t = 0 was estimated from extrapolation of the ln([**3**]) to the total concentration of all species measured in solution, in accordance with the law of mass conservation. Substituting $k_{obs}^{\mathbf{3}}$ determined from ln([**3**]) vs. time data in equations x and y and adjusting the time for the calculated t = 0 allowed for $k_{obs}^{\mathbf{10}}$ to be determined from a two parameter fit to either equation using the "General Fit" function in the Kaleidagraph™ v. 3.6 software (based on the Levenberg-Marquardt algorithm). The $k_{obs}^{\mathbf{10}}$ that is reported in Table S2 is a composite average of the two rate constants determined from [**4**] and [**10**] vs. time data. The observed rate constants for the formation of **8** and **9** via intermediate **7** ($k_{obs}^{\mathbf{7}}$) could be estimated in a similar fashion using equation x and [**7**] vs. time data, but fits for the [**8**] vs. time data using equation y were poor. As discussed in the main text of the article, we believe that this is due to the competing direct pathway from **3** to **8** that is not accounted for by equation y. The elementary rate constants for all pathways were determined from the observed rate constants and the final concentration of species in solution as determined by NMR or by GC using equations (S-3)-(S-5):

$$\frac{k_6^{\mathbf{3}}}{k_5^{\mathbf{3}}} = \frac{[\mathbf{10}]+[\mathbf{11}]+[\mathbf{4}]}{[\mathbf{7}]+[\mathbf{8}]+[\mathbf{9}]} \quad \text{(S-3)}$$

$$\frac{k_6^{\mathbf{10}}}{k_5^{\mathbf{10}}} = \frac{[\mathbf{11}]}{[\mathbf{4}]} \quad \text{(S-4)}$$

$$\frac{k_5^{\mathbf{7}}}{k_{hydrolysis}^{\mathbf{7}}} = \frac{[\mathbf{8}]}{[\mathbf{9}]} \quad \text{(S-5)}$$

Representative data for the determination of $k_{obs}^{\mathbf{3}}$, $k_{obs}^{\mathbf{10}}$, and $k_{obs}^{\mathbf{7}}$ determined in this fashion appear in Figures S2, S3, and S4, and the average elementary rate constants appear in Table S2 for comparison with simulated data.

Figure S2. *Representative semilog plot and fit via regression analysis for species **3** in reaction of **3** in D_2O at 70 °C.*

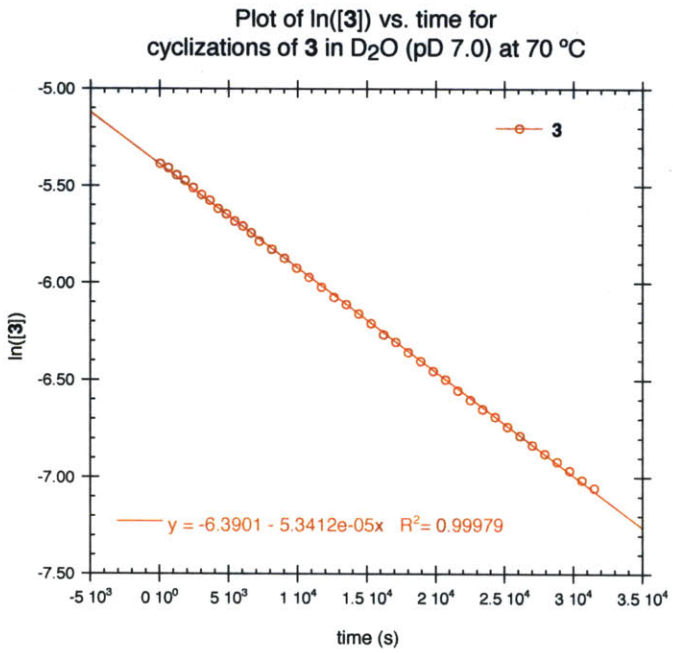

Plot of ln([3]) vs. time for
cyclizations of 3 in D2O (pD 7.0) at 70 °C
-5.00
-5.50
-6.00
-6.50
-7.00
-7.50
ln([3])
3
y = -6.3901 - 5.3412e-05x R2= 0.99979
-5 10^3
0 10^0
5 10^3
1 10^4
1.5 10^4
2 10^4
2.5 10^4
3 10^4
3.5 10^4
time (s)

Figure S3. *Representative concentration vs. time data and fits via regression analysis for species* ***10*** *(left) and* ***4*** *(right) in cyclization of* ***3*** *in D_2O at 70 °C.*

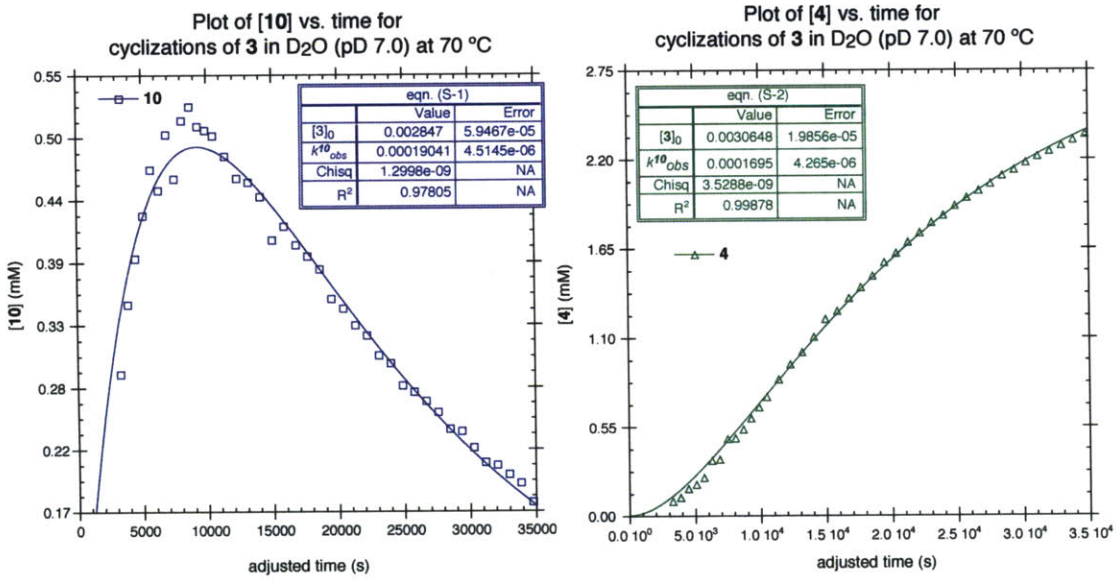
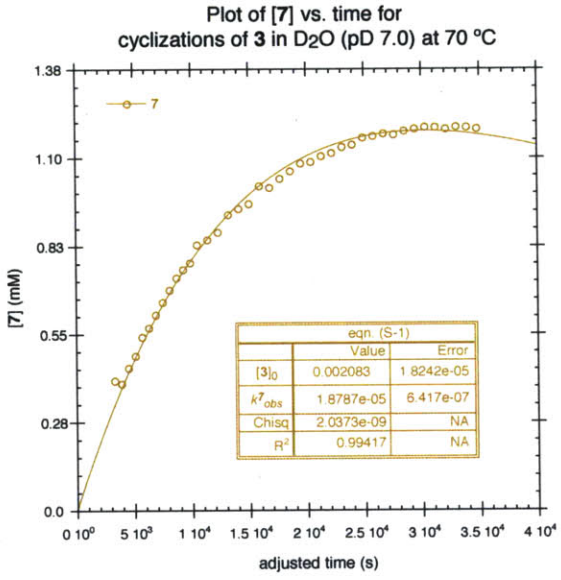


Figure S4. *Representative concentration vs. time data and fits via regression analysis for species 7 in cyclization of* ***3*** *in D_2O at 70 °C.*



Determination of rate constants for cyclization of diepoxide 3 using computer simulation. Due to the complexity of the reaction, we reasoned that the best estimation of rate constants for the cyclization of diepoxide **3** would be obtained using the complex reaction simulation program COPASI.[19] Rate constants for all steps could be determined from the concentration vs. time data for all species measured using the "Parameter Estimation" protocol assuming all reactions are irreversible. The method used for the simulation was the Levenberg-Marquardt method, with an iteration limit of 500 and a tolerance of $1x10^{-5}$. The initial concentration of all species was estimated using the first data point in the NMR data. The results from the simulations were the same regardless of whether each parameter was optimized individually or if all parameters were allowed to

freely vary. To ensure that the estimated parameters were not local minima, each rate constant was randomly varied and the simulation was repeated. Simulations were also carried out assuming that no direct pathway from **3** to **8** existed (i.e. without k_{55}^3), but the experimental data could not be satisfactorily simulated. Fits for [**8**] vs. time data were particularly poor when k_{55}^3 was excluded (see Figure S5 and Table S1 for representative data and fits for a representative kinetics run).

Figure S5. *Representative simulations for cyclization of* ***3*** *in D_2O (pD 7.0) at 70 °C including (left) and excluding (right) k^3_{55} in the simulation.*

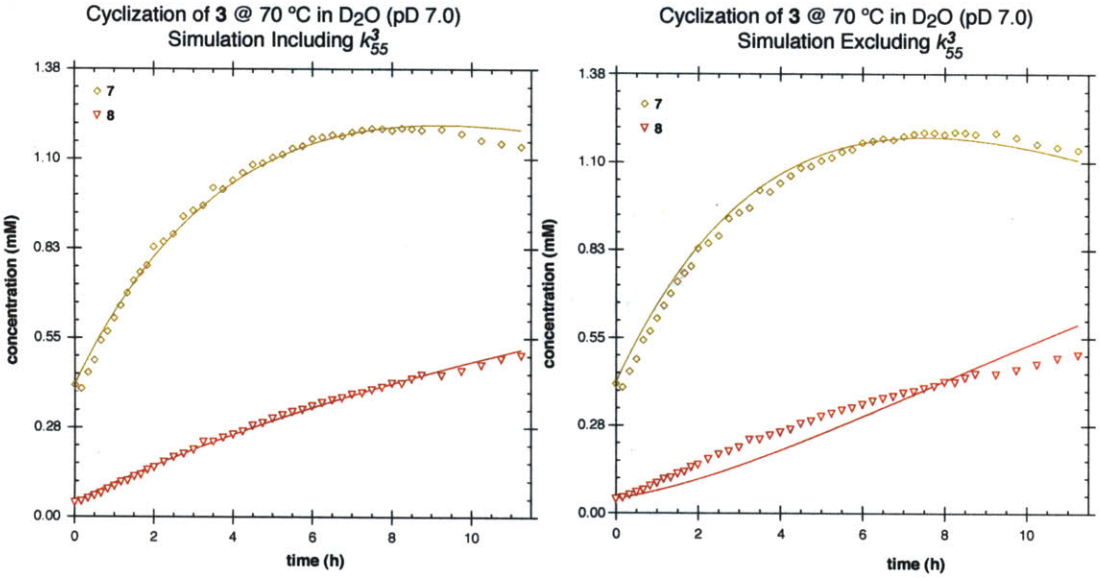


Table S1. *Comparison of simulations for cyclizations of* ***3*** *for simulations excluding and including* k^3_{55}.

		without k^3_{55}		with k^3_{55}	
		simulation	coeff. var.	simulation	coeff. var.
k^3	k_{obs}	5.31E-05	-	5.36E-05	-
	k_6/k_5	1.79	-	1.73	-
	k_6	3.26E-05	0.11	3.27E-05	0.05
	k_5	1.82E-05	0.40	1.57E-05	0.25
	k_{dir}	-	-	3.17E-06	1.22
	$k_{hydrolysis}$	2.30E-06	2.82	1.99E-06	1.66
k^{10}	k_{obs}	2.19E-04	-	2.19E-04	-
	k_6/k_5	15.1	-	15.1	-
	k_6	2.05E-04	0.27	2.05E-04	0.13
	k_5	1.36E-05	1.12	1.36E-05	0.54
k^7	k_{obs}	1.02E-05	-	1.02E-05	-
	$k_5/k_{hdyrolysis}$	3.50	-	1.17	-
	k_5	1.32E-05	0.45	5.49E-06	1.88
	$k_{hydrolysis}$	3.77E-06	7.43	4.68E-06	2.85
		objective	mean err.	objective	mean err.
species conc.	3	1.68E-10	5.56E-07	1.38E-10	-1.51E-07
	10	3.75E-10	-4.78E-07	3.78E-10	-5.77E-07
	7	4.56E-10	1.19E-06	2.79E-10	2.66E-07
	4	1.00E-10	6.18E-07	8.32E-11	3.86E-07
	11	6.62E-12	1.59E-07	5.51E-12	9.94E-08
	8	4.36E-09	-4.55E-06	1.29E-10	2.49E-07
	9+12	2.37E-10	-2.94E-07	2.25E-10	-7.18E-07
	expt.	5.70E-09	-3.98E-07	1.24E-09	-6.37E-08

Discussion of rate constants determined from simulation vs. regression analysis. Rate constants determined from the simulations including k^3_{55} appear in Table S2 for comparison with those determined from regression analysis. Rate constants determined from simulation agree reasonably well with those determined by regression analysis for the first step kinetics (k^3_x), with differences in elementary rate constants likely due to the inclusion of k^3_{55} and $k^3_{hydrolysis}$ in the simulation but not accounted for in the regression analysis. The data from the two methods agree less well for the "second step" kinetics (k^{10}_x and k^7_x), especially for k^7_x. Regression analysis consistently results in smaller k^{10}_{obs} and larger k^7_{obs} than what results from simulation. The discrepancies are likely due to the inclusion of the side reactions in the simulation and to the error associated with determining t = 0 for regression analysis (*vide supra*). Additionally, significant error in k^7_x is expected for both simulation and regression analysis, as this reaction had not sufficiently progressed during the data collection time frame. We therefore conclude that the rate constants determined from simulation and from regression analysis agree to first approximation.

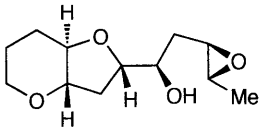
Table S2. *Comparison of rate constants determined from regression analysis or by simulation for cyclizations of* ***3.***

		regression analysis	avg. err.	simulated	avg. err.
k^3	k_{obs}	5.22E-05	1.93E-06	5.30E-05	1.45E-06
	k_6/k_5	1.59	0.03	1.97	0.15
	k_6	3.20E-05	1.37E-06	3.16E-05	1.22E-06
	k_5	2.02E-05	5.62E-07	1.61E-05	6.00E-07
	k_{55}	-	-	3.08E-06	2.51E-07
	$k_{hydrolysis}$	-	-	2.17E-06	5.80E-07
k^{10}	k_{obs}	1.83E-04	2.67E-06	2.33E-04	9.38E-06
	k_6/k_5	15.2	0.2	15.2	0.2
	k_6	1.71E-04	2.39E-06	2.18E-04	8.89E-06
	k_5	1.12E-05	2.73E-07	1.43E-05	6.44E-07
k^7	k_{obs}	1.92E-05	4.44E-07	1.04E-05	9.09E-07
	$k_5/k_{hydrolysis}$	1.35	0.04	1.50	0.12
	k_5	1.10E-05	2.97E-07	6.18E-06	3.22E-07
	$k_{hydrolysis}$	8.20E-06	1.88E-07	4.18E-06	5.87E-07

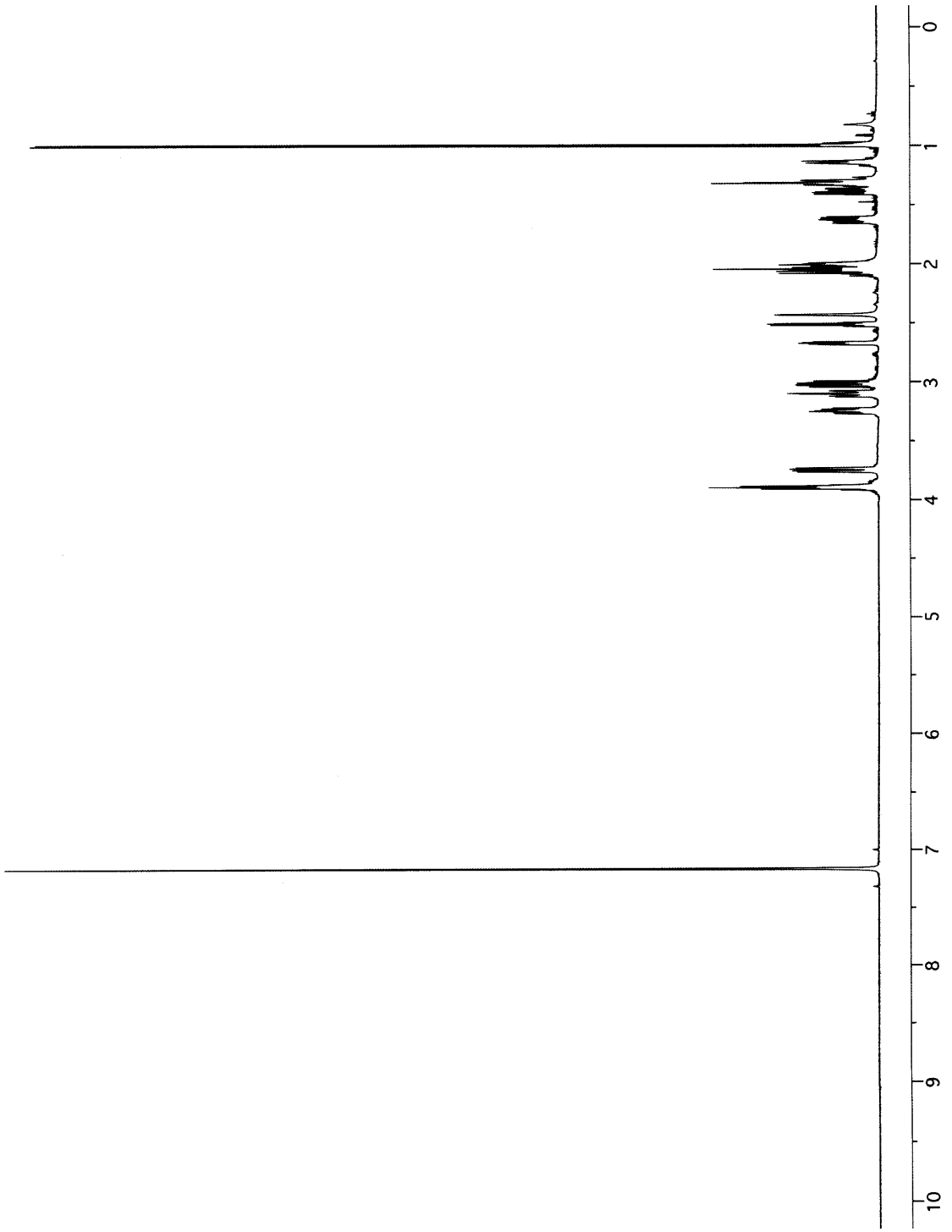
Comparison of rate constants from simulation with those obtained for monoepoxides. The "second step" rate constants (k_x^{10} and k_x^7) determined from simulation of data from cyclizations of **3** agree with rate constants determined from independent cyclizations of **7** and **10**. Observed and elementary rate constants determined for cyclization from isolated **10** are within experimental error as compared to those determined from simulation of diepoxide **3**. Although k_{obs}^7 determined for cyclization of isolated **7** are comparable to the equivalent rate constant determined from cyclization of diepoxide **3**, the elementary rate constants are different. This discrepancy is likely due to the overlapping resonances of **9** and **12** in spectra of the reaction of **3**, which results in significant error in determining the relative contributions of $k_{hydrolysis}^3$ and $k_{hydrolysis}^7$. Considering this complication, we consider the data obtained from the monoepoxides **7** and **10** to be in agreement with those obtained from diepoxide **3**.

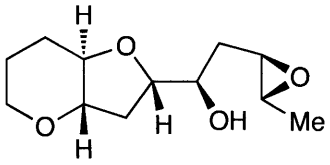
Table S3. *Comparison of rate constants determined from cyclizations of diepoxide* ***3*** *and monoepoxides* ***7*** *and* ***10.***

		avg. from **3**		avg. from **10** and **7**	
		k (s^{-1})	error	k (s^{-1})	error
k^{10}	k_{obs}	2.33E-04	9.38E-06	2.67E-04	2.62E-05
	k_6/k_5	15.2	0.2	18.5	1.3
	k_6	2.18E-04	8.89E-06	2.54E-05	2.58E-05
	k_5	1.43E-05	6.44E-07	1.36E-05	4.63E-07
k^7	k_{obs}	1.04E-05	9.09E-07	1.15E-05	1.00E-07
	$k_5/k_{hydrolysis}$	1.50	0.12	0.56	0.01
	k_5	6.18E-06	3.22E-07	2.90E-06	8.37E-08
	$k_{hydrolysis}$	4.18E-06	5.87E-07	5.15E-06	1.17E-07



7





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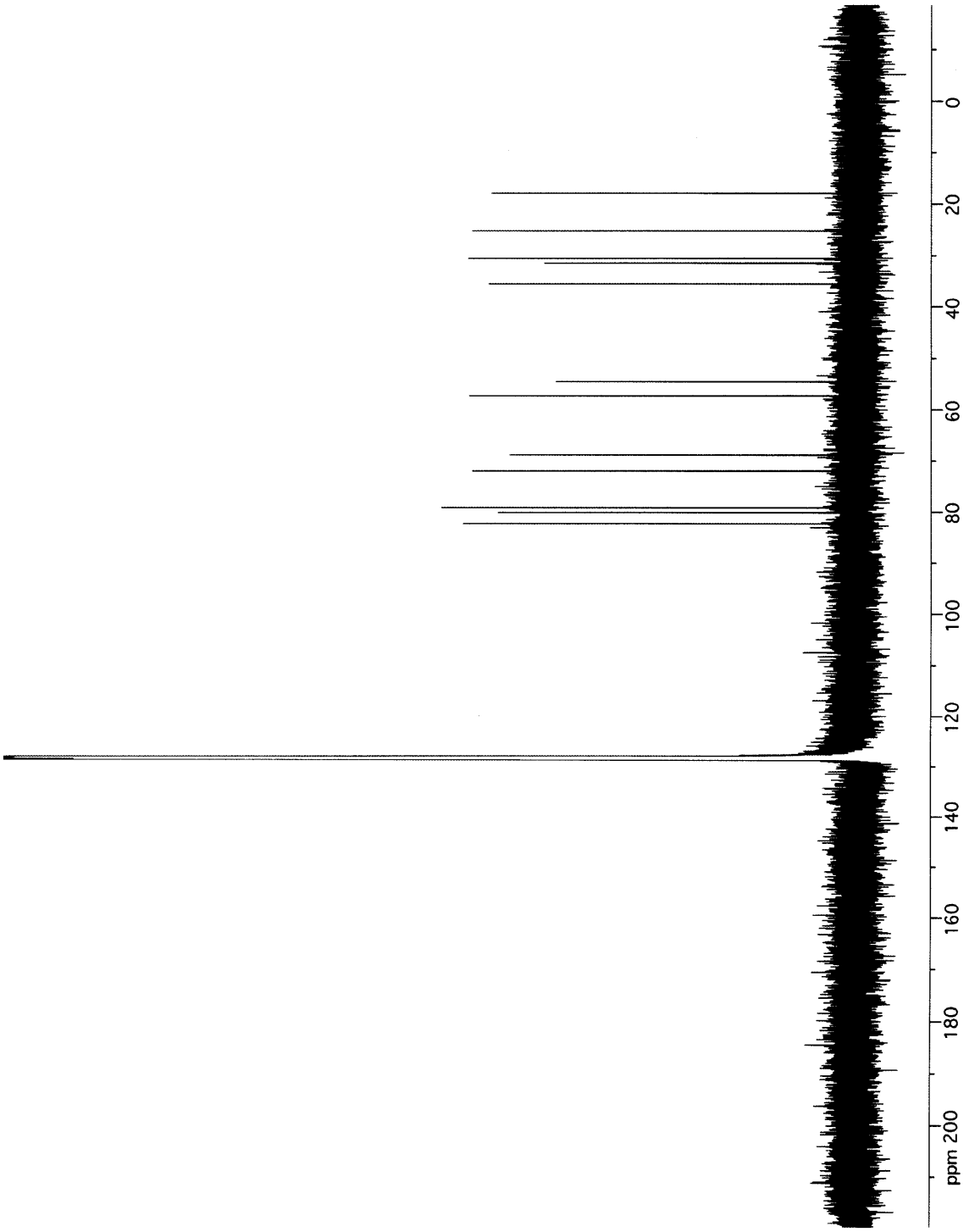

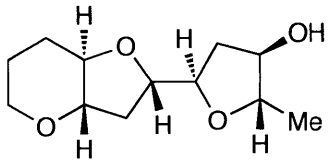

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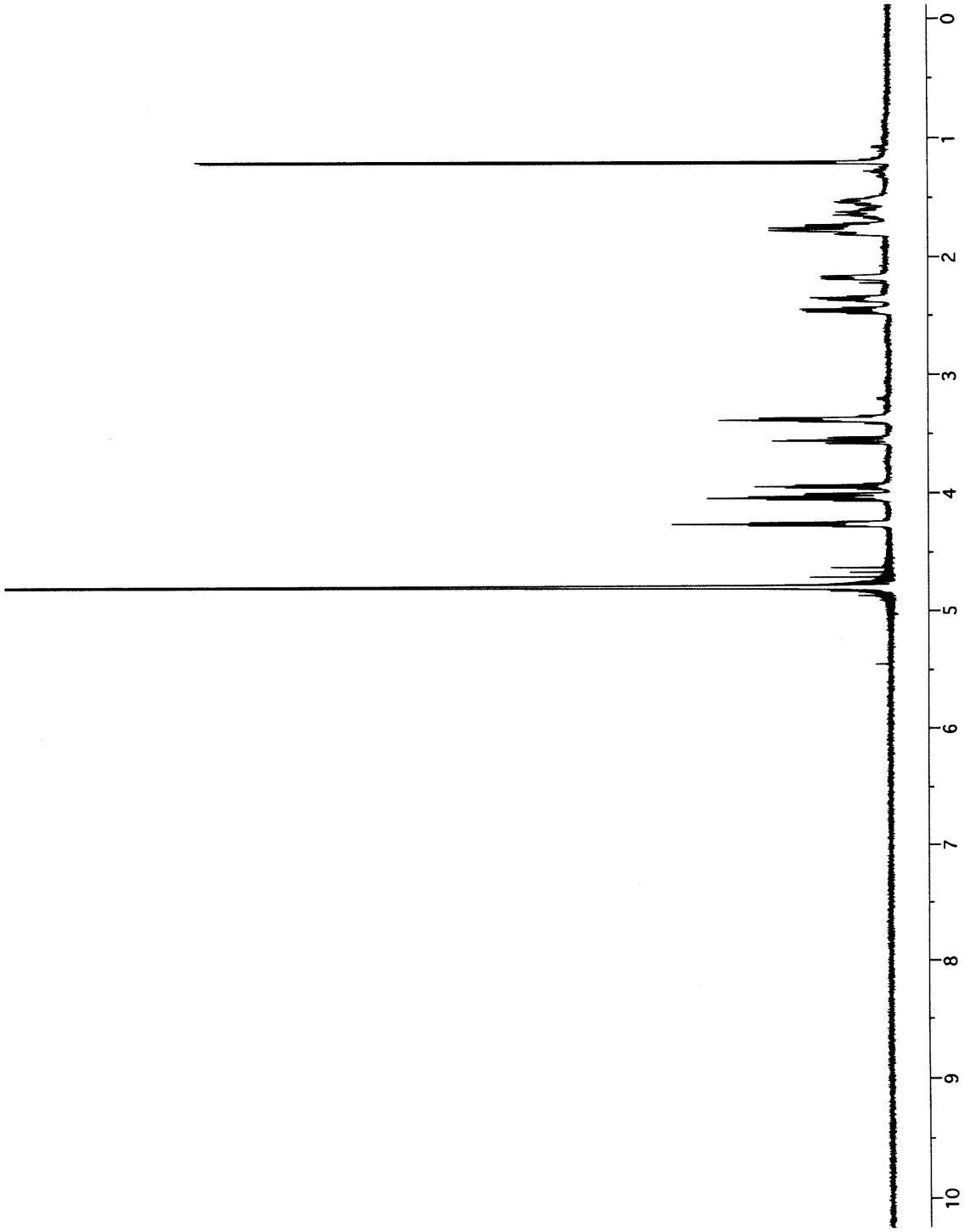

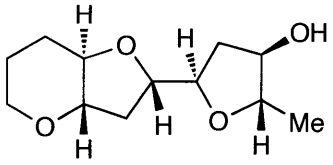

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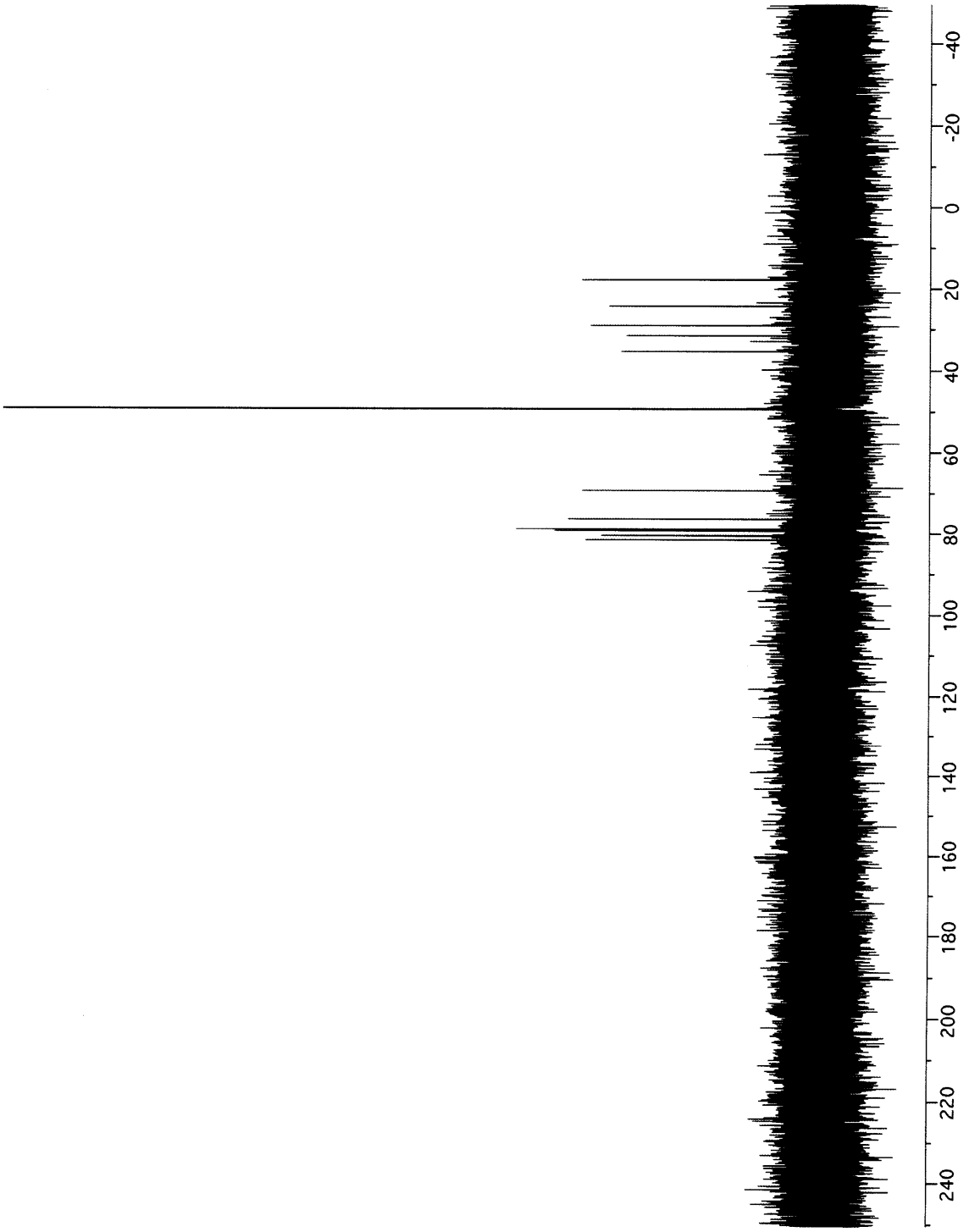

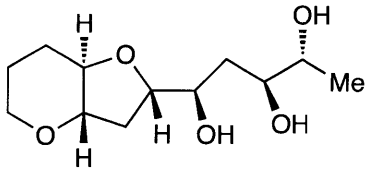

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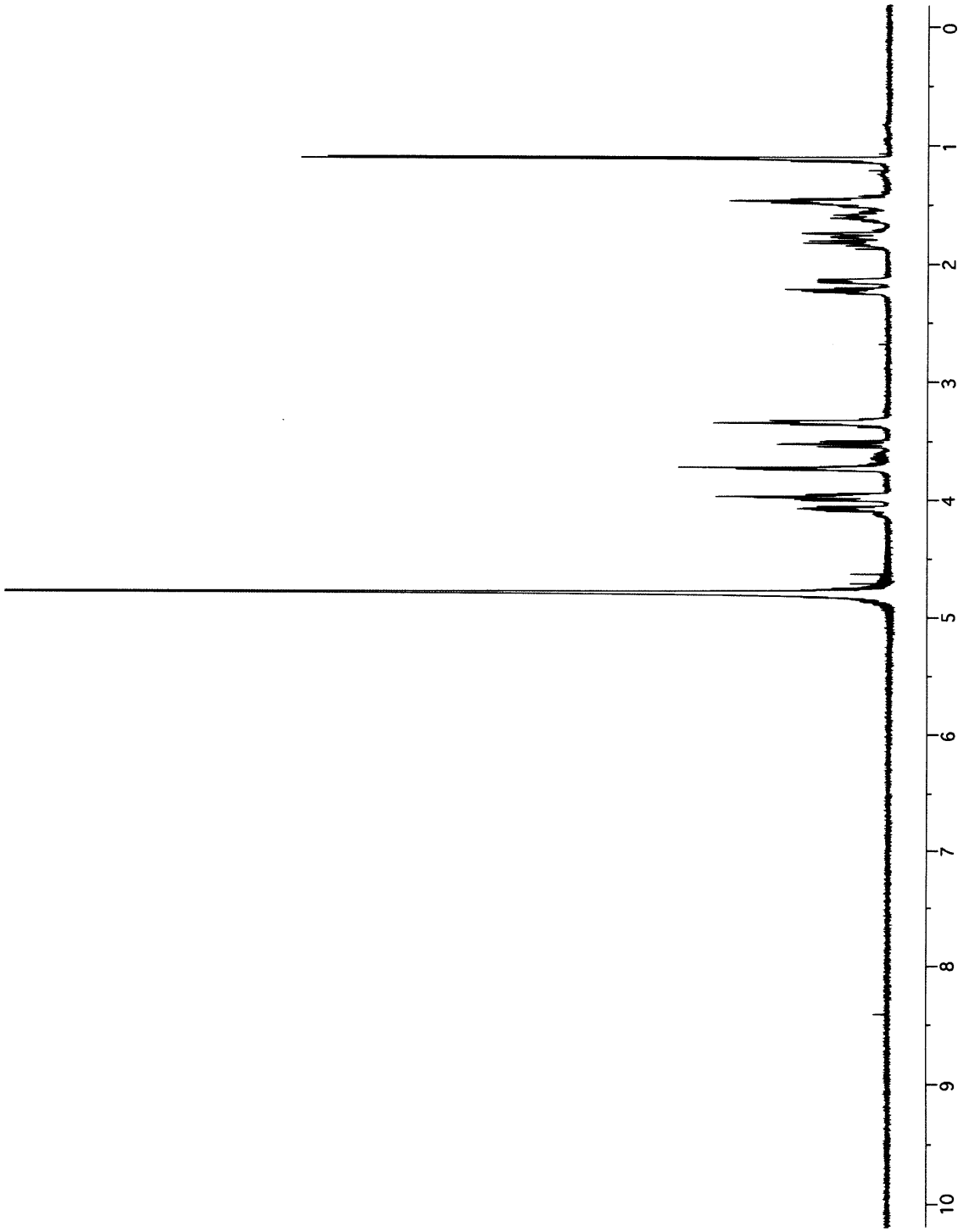

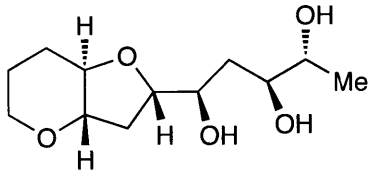
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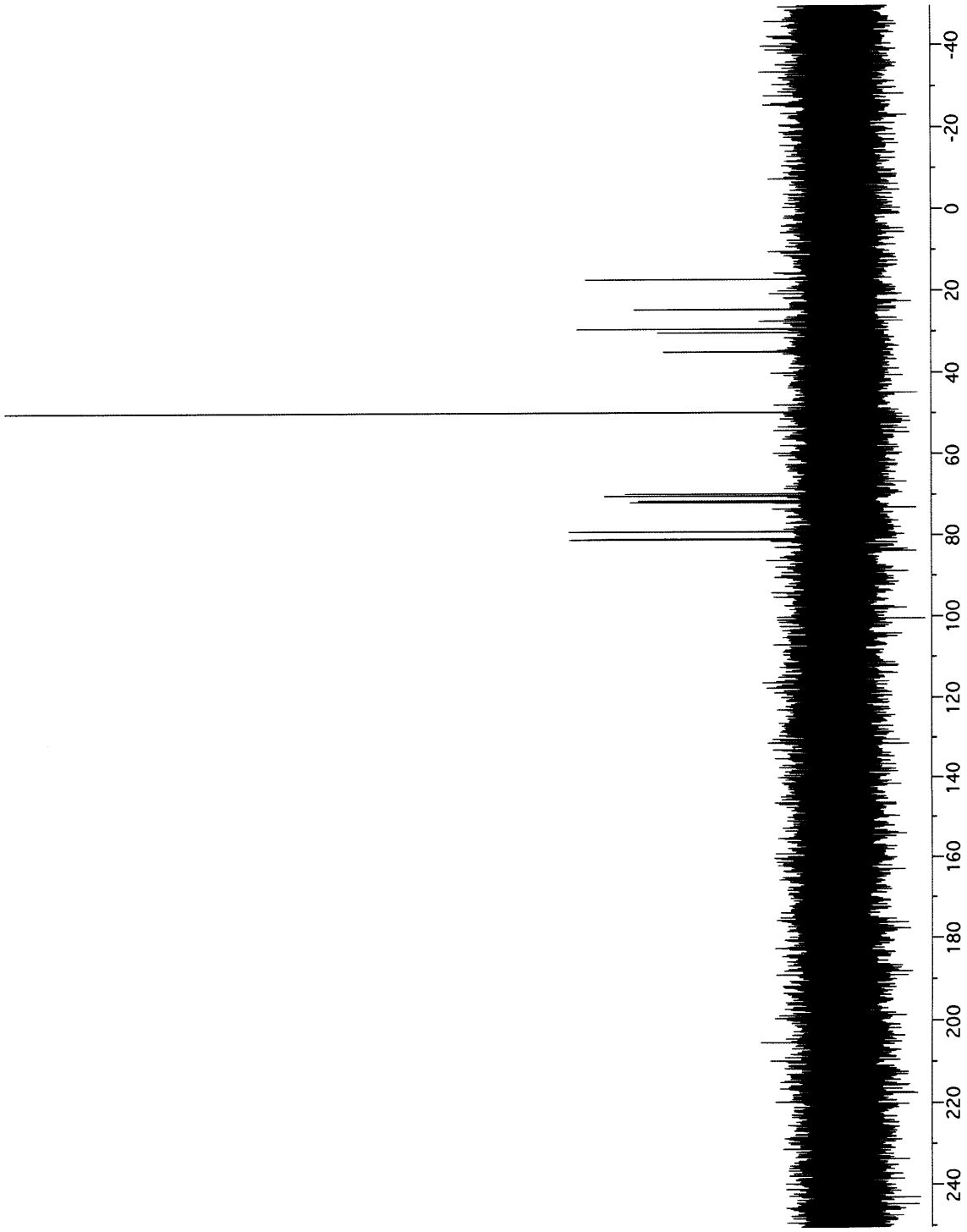
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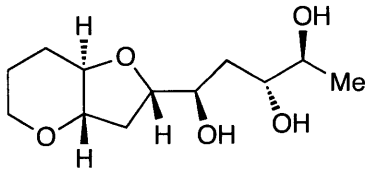

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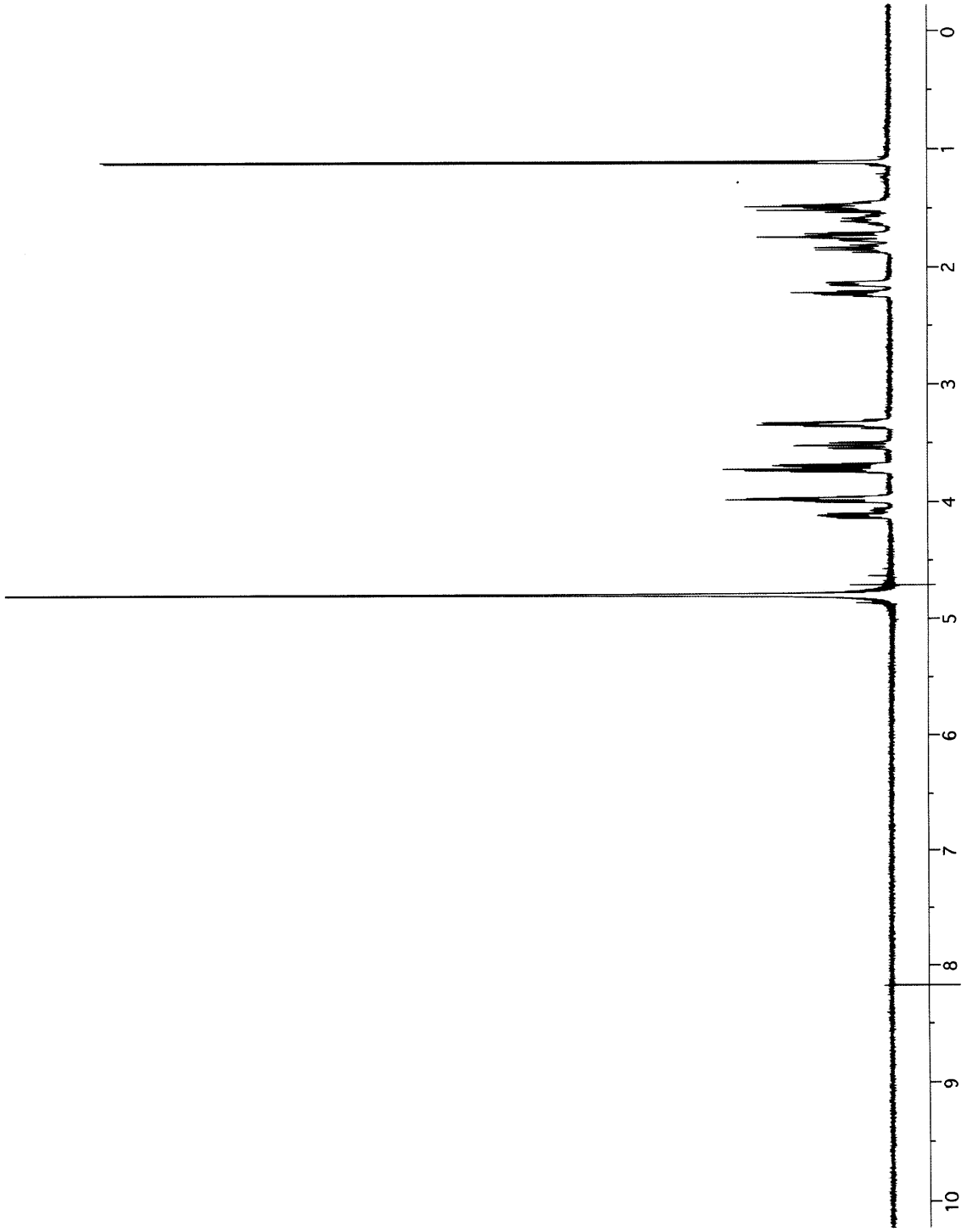

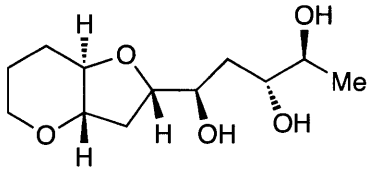
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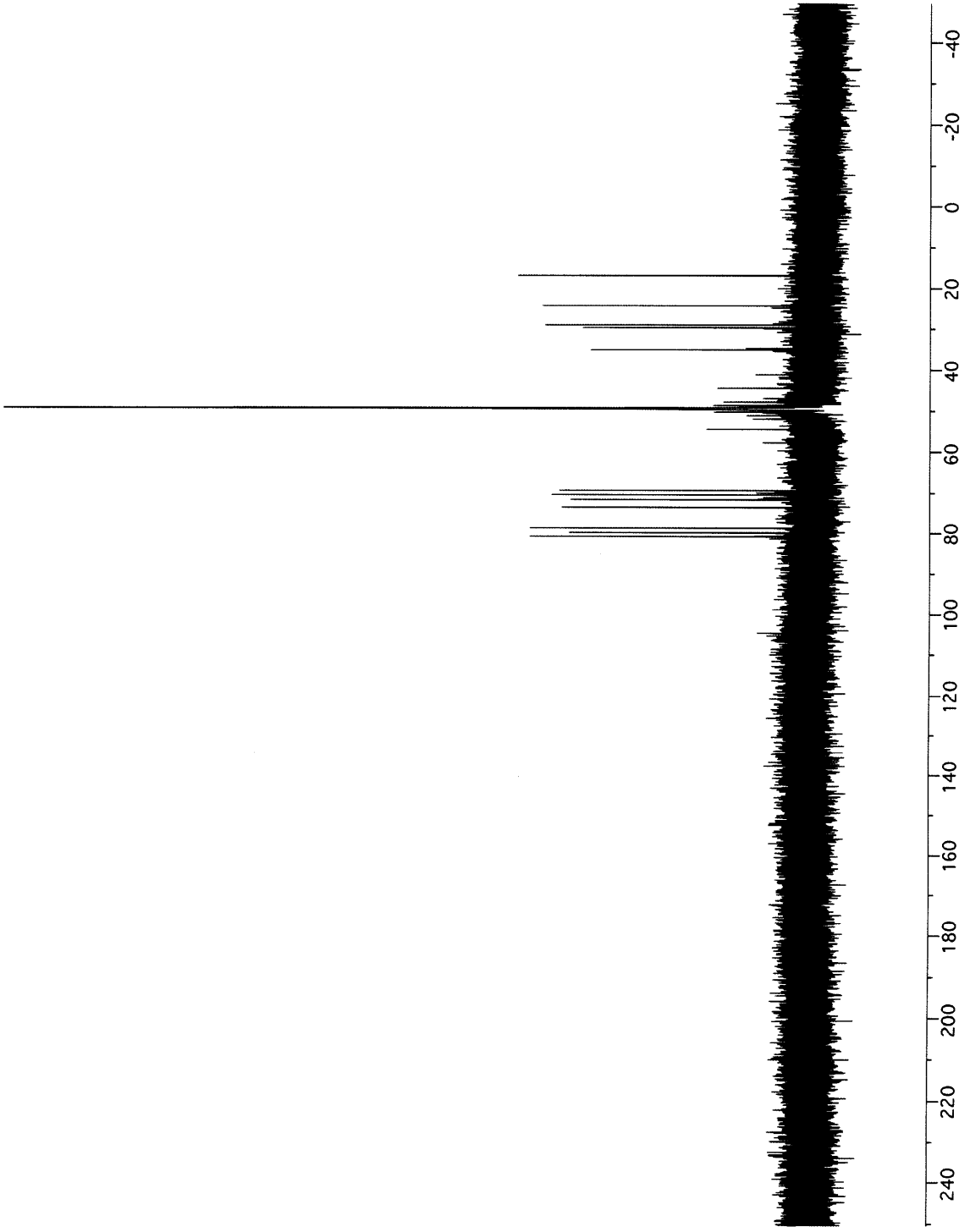
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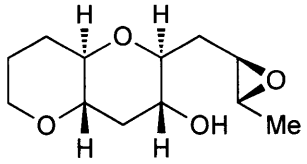

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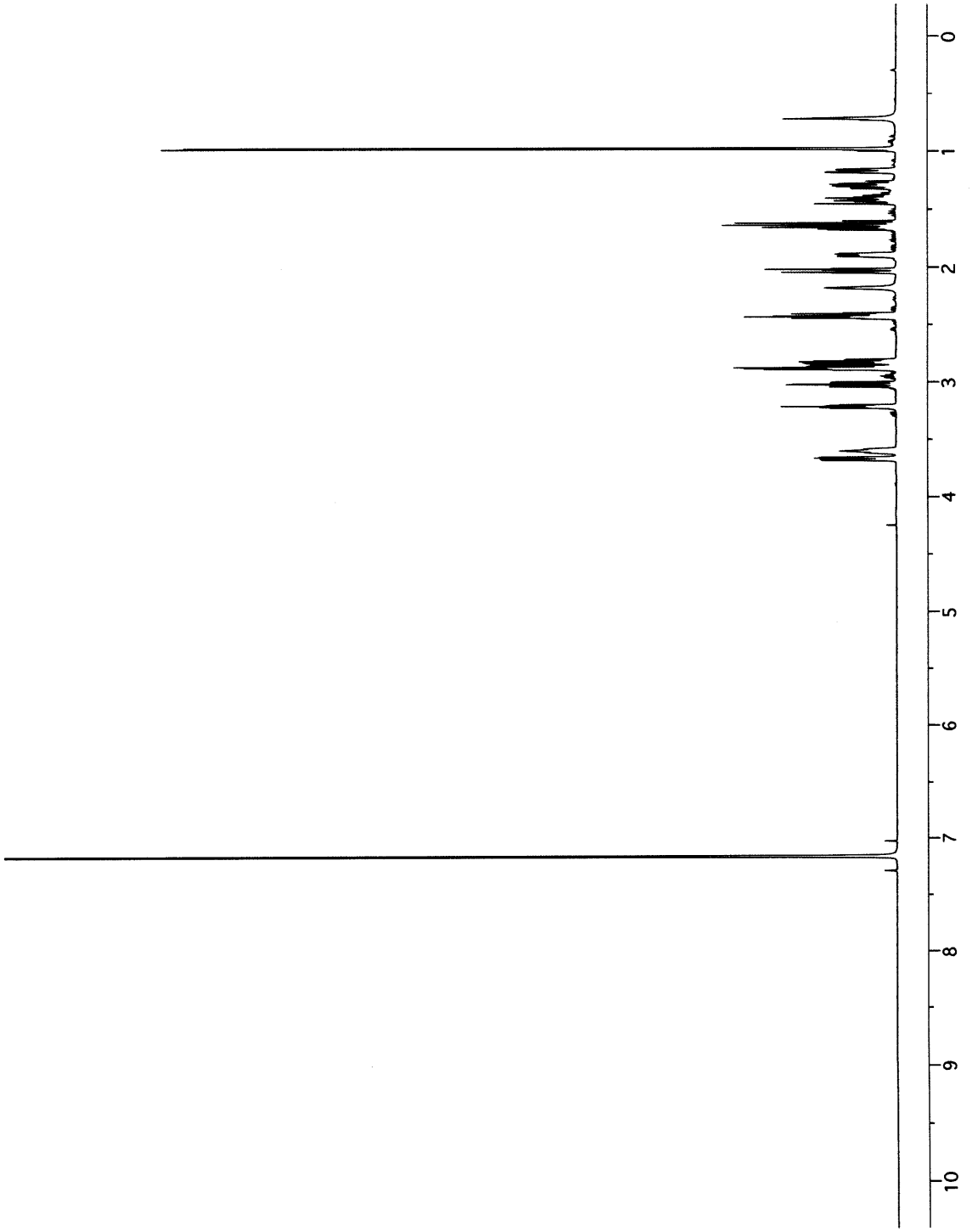

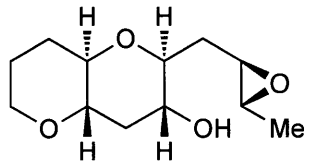

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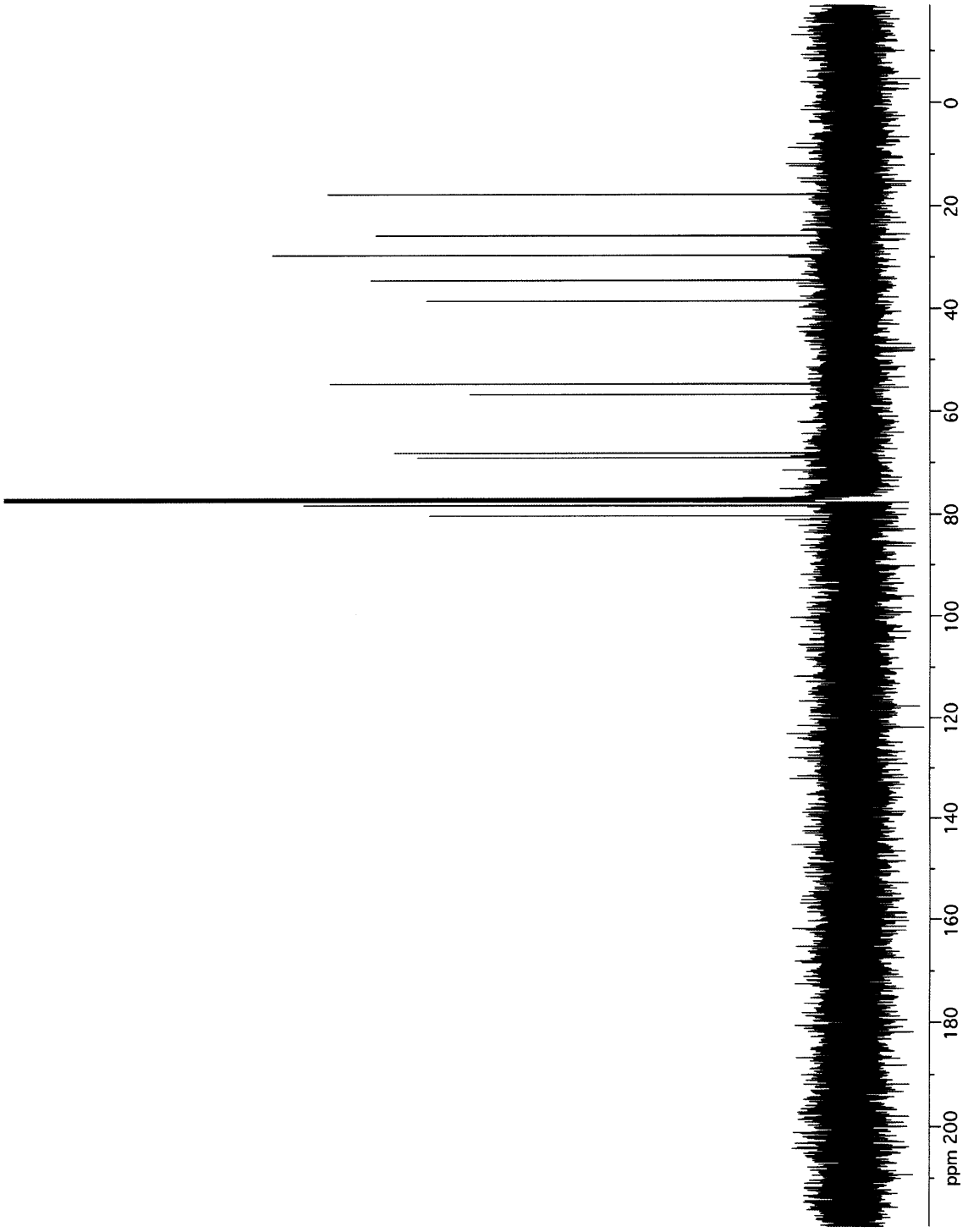

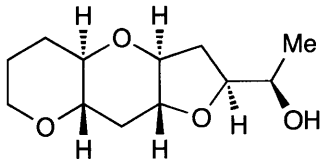

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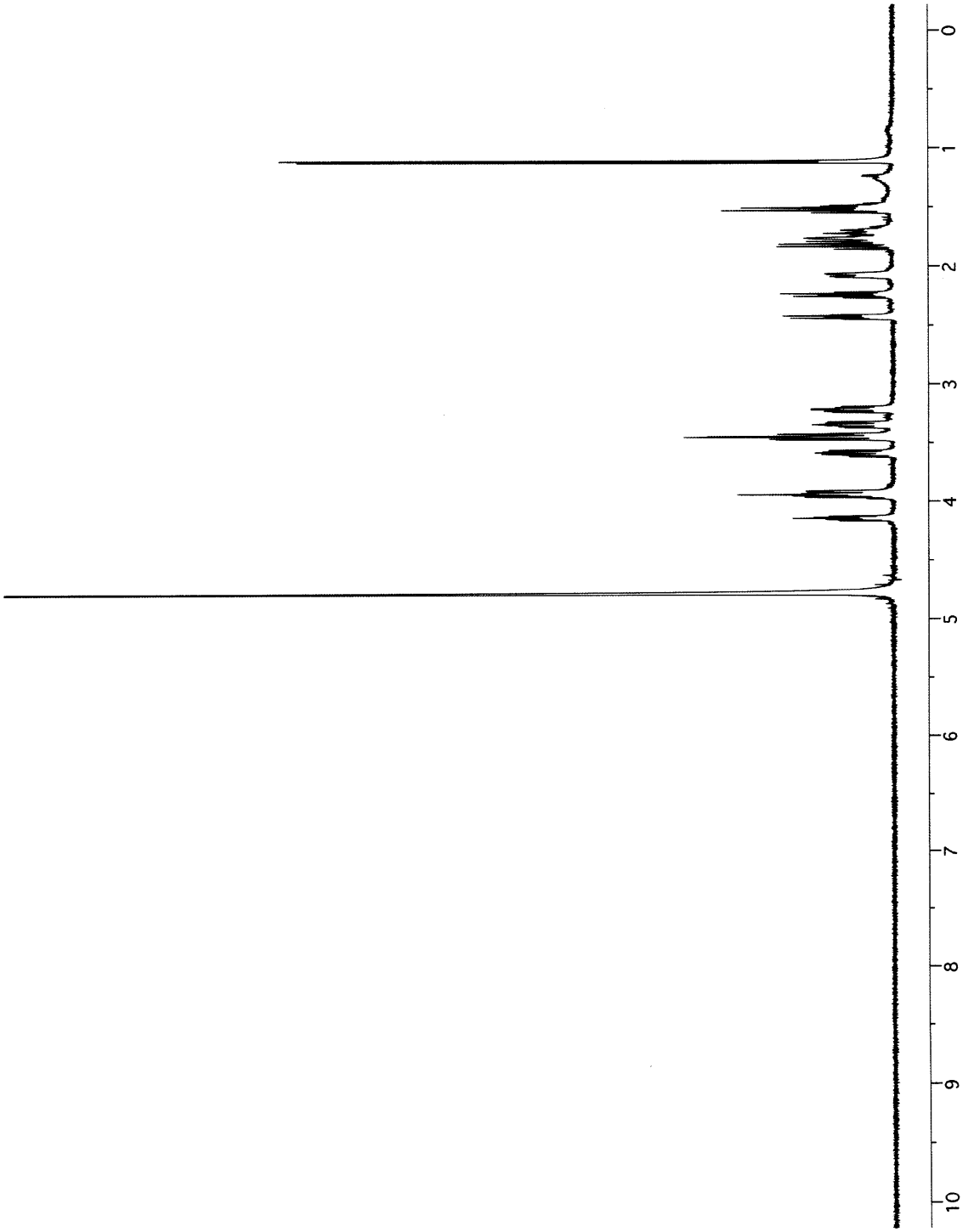

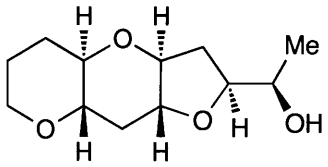

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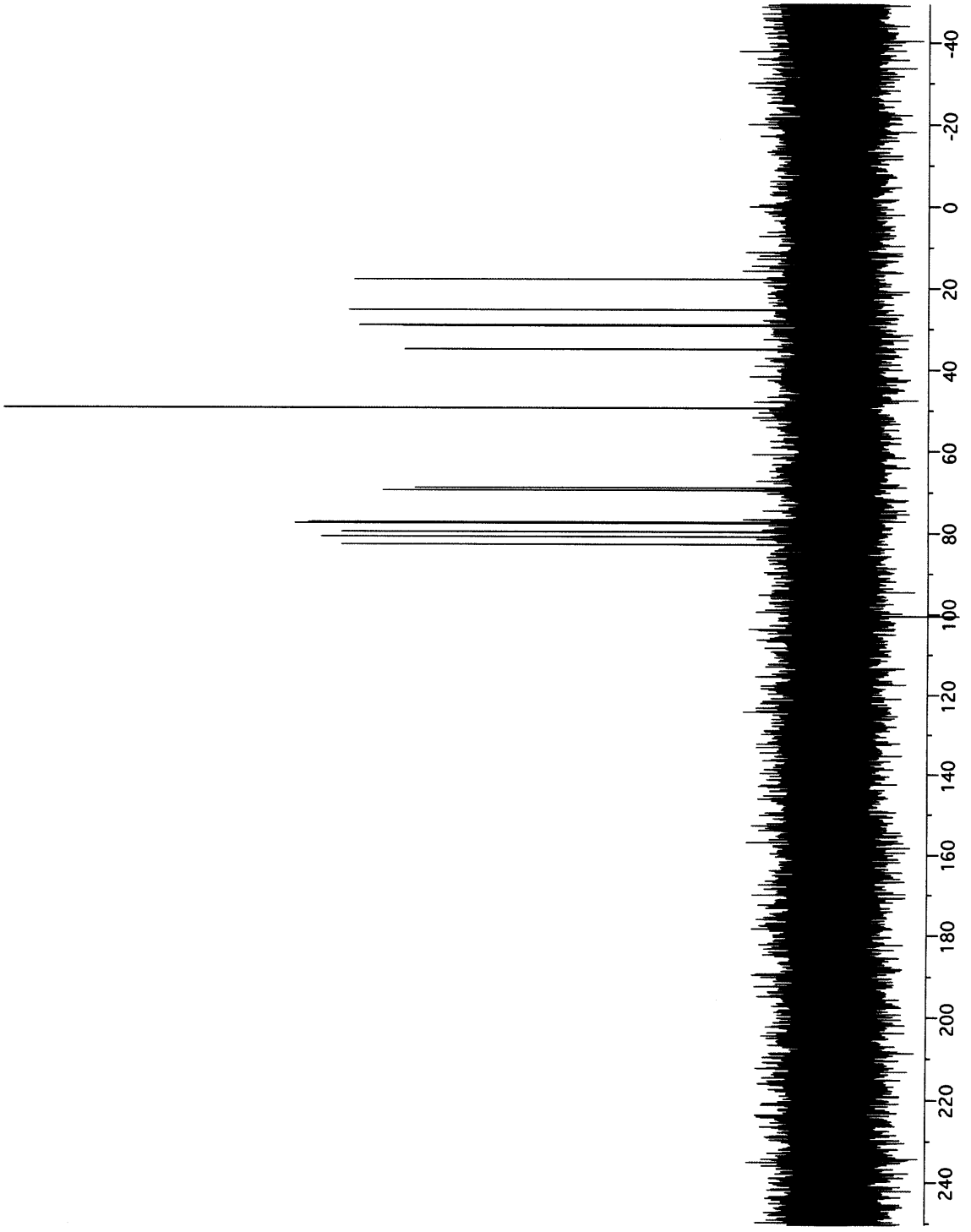

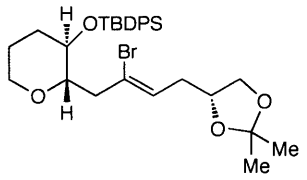

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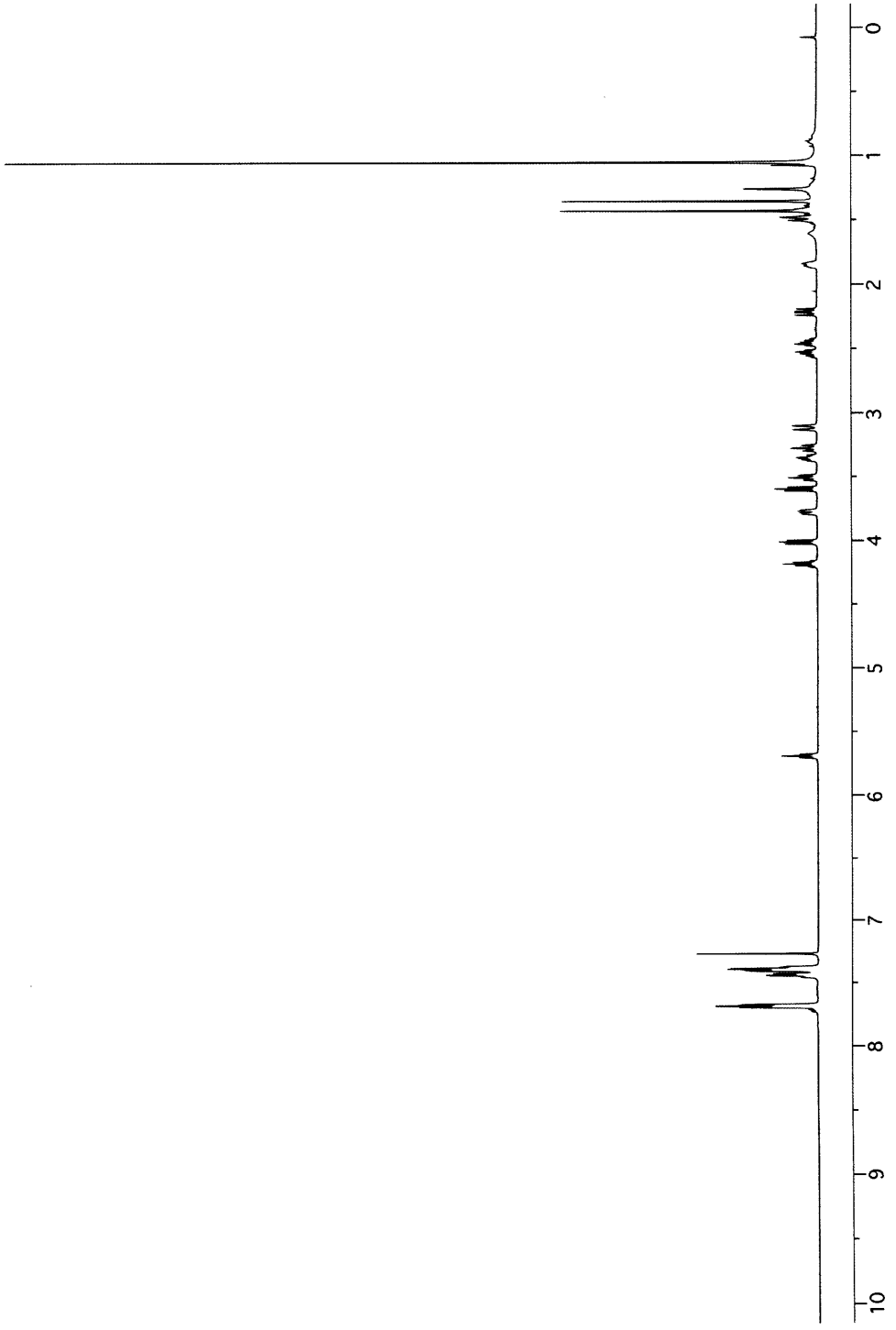

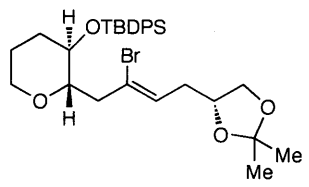

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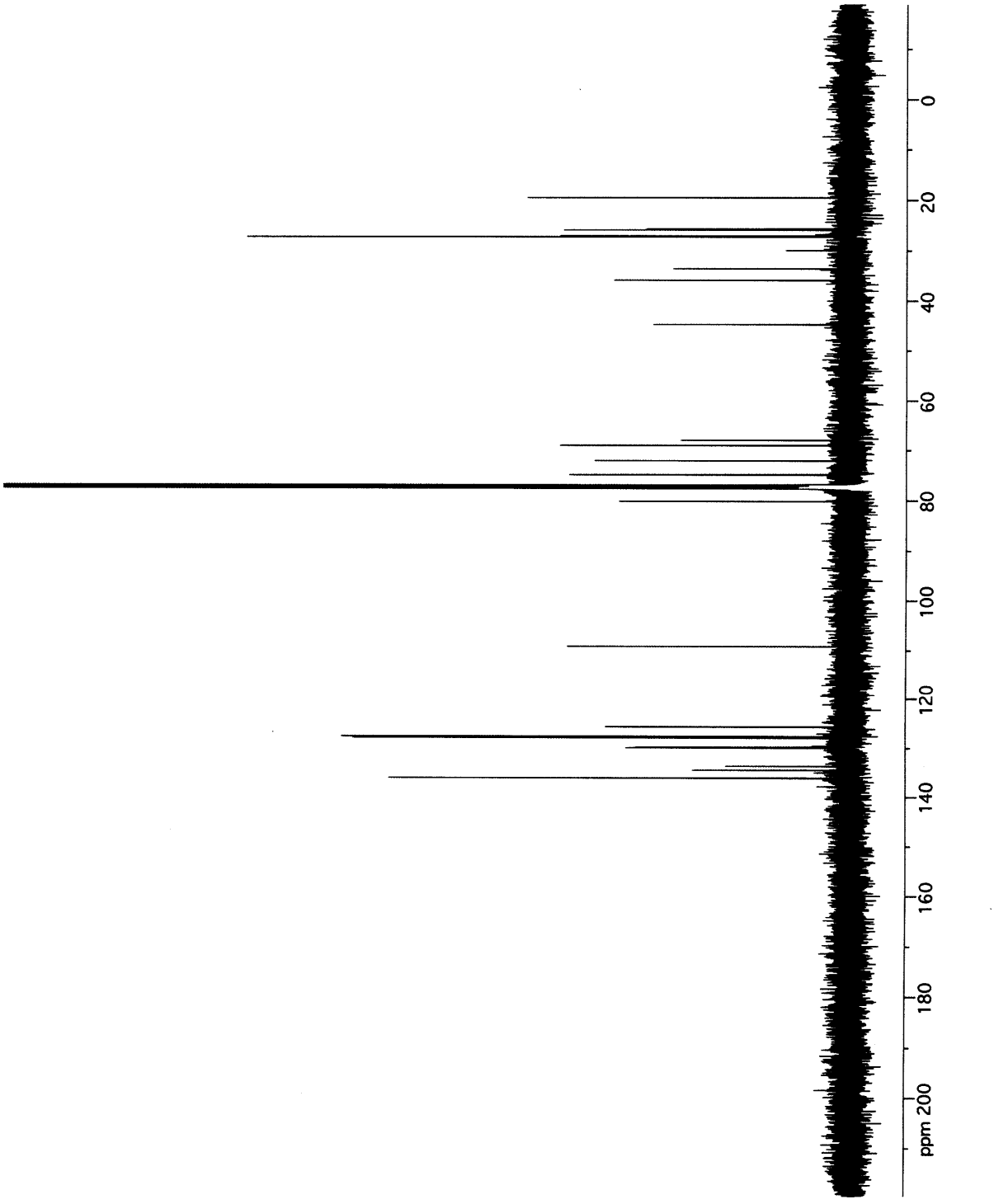

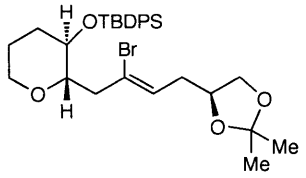

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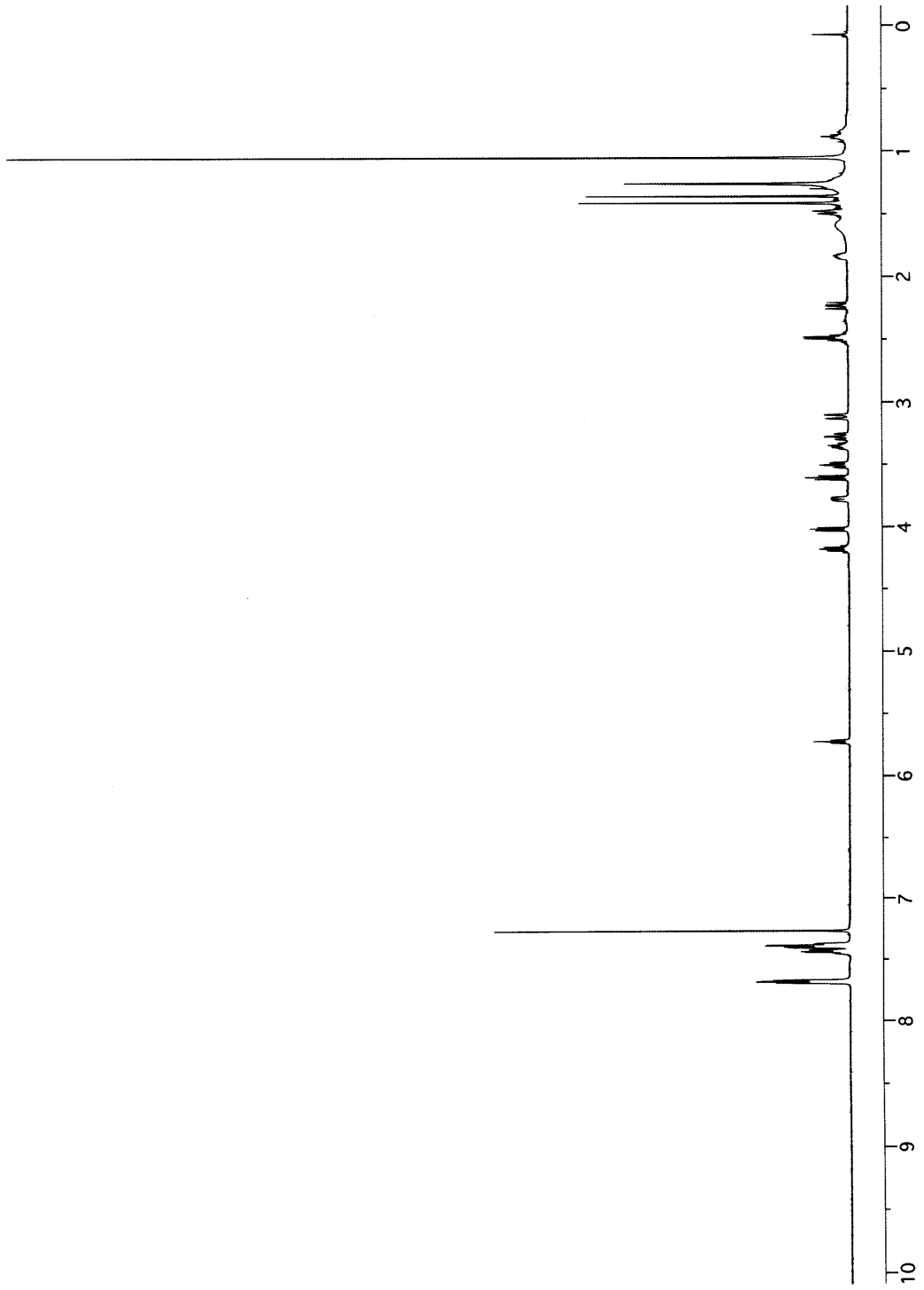

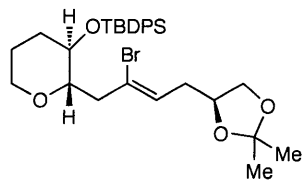

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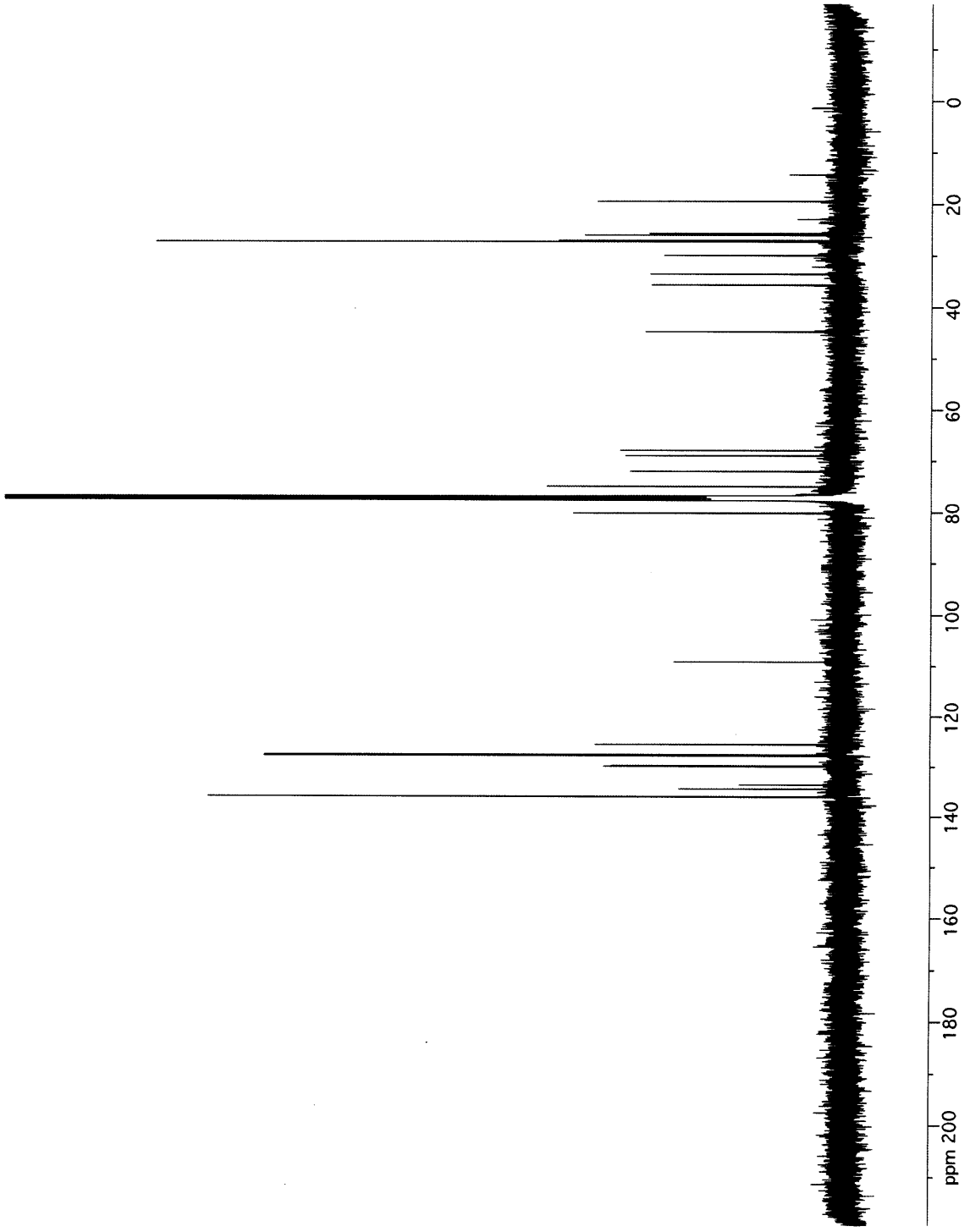

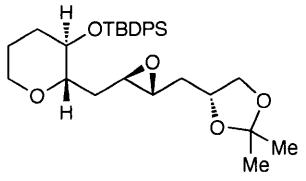

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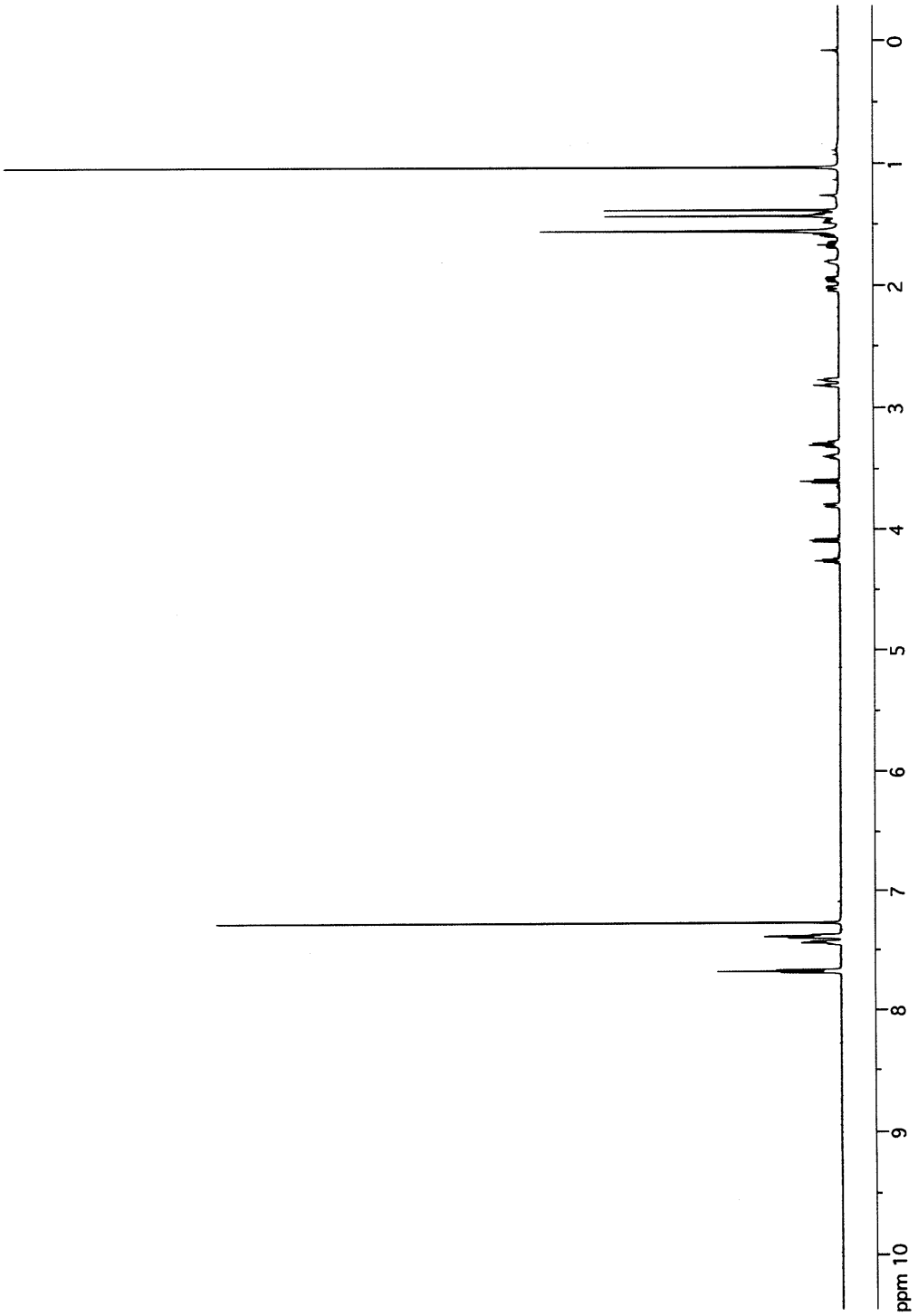

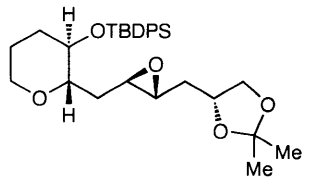

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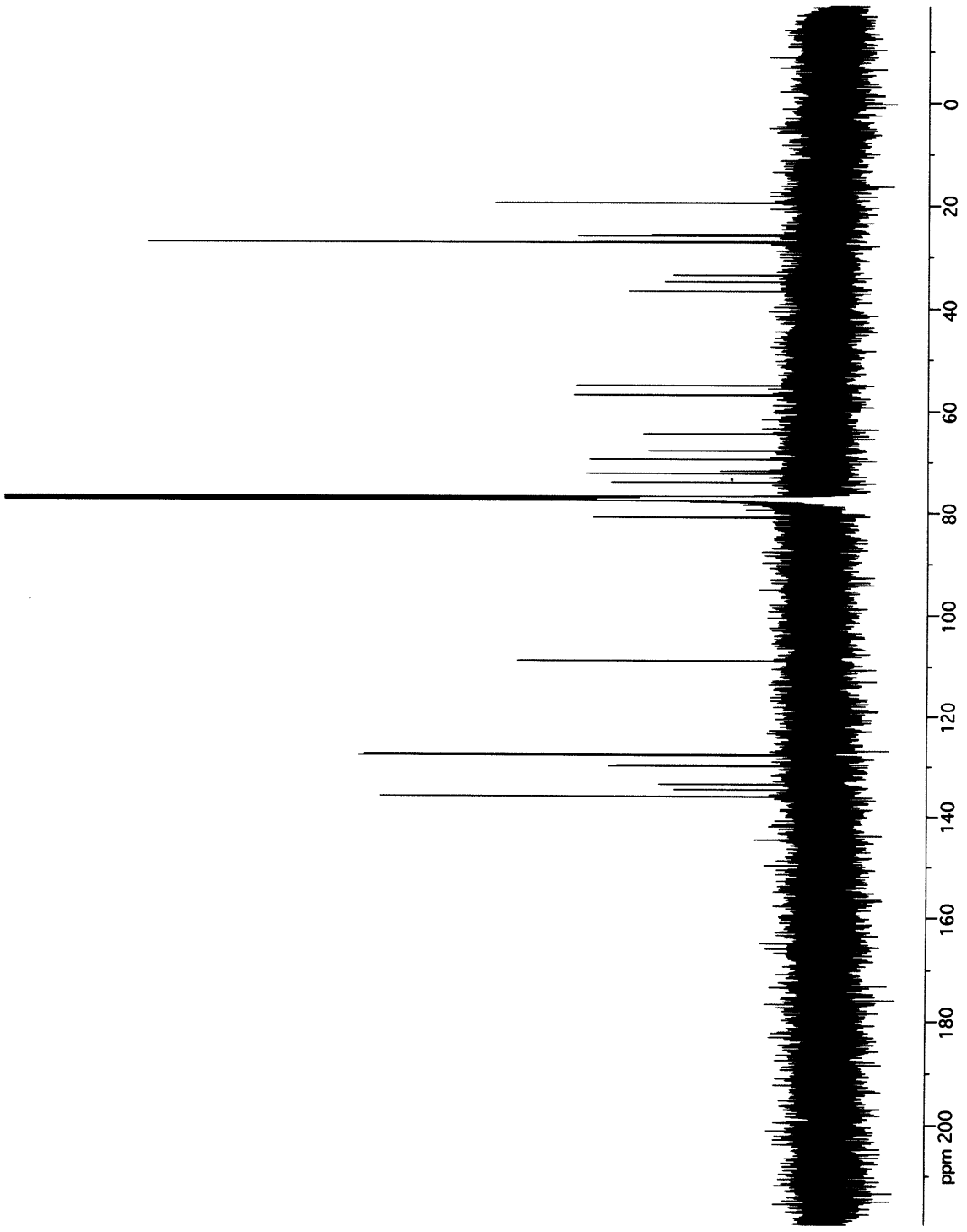

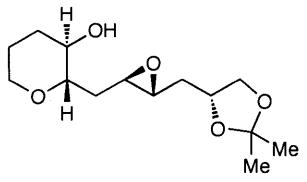

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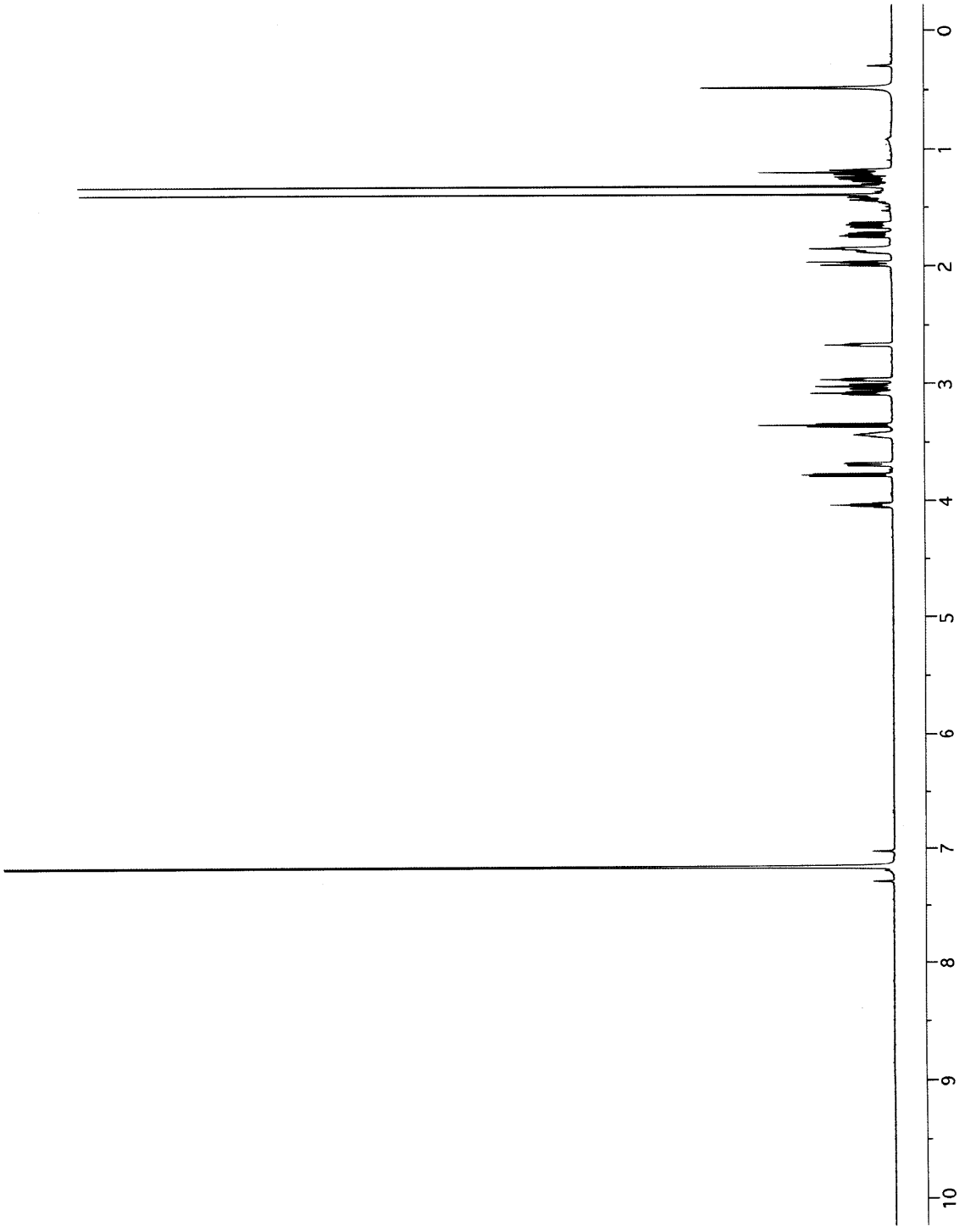

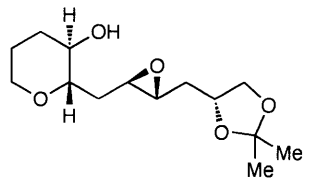

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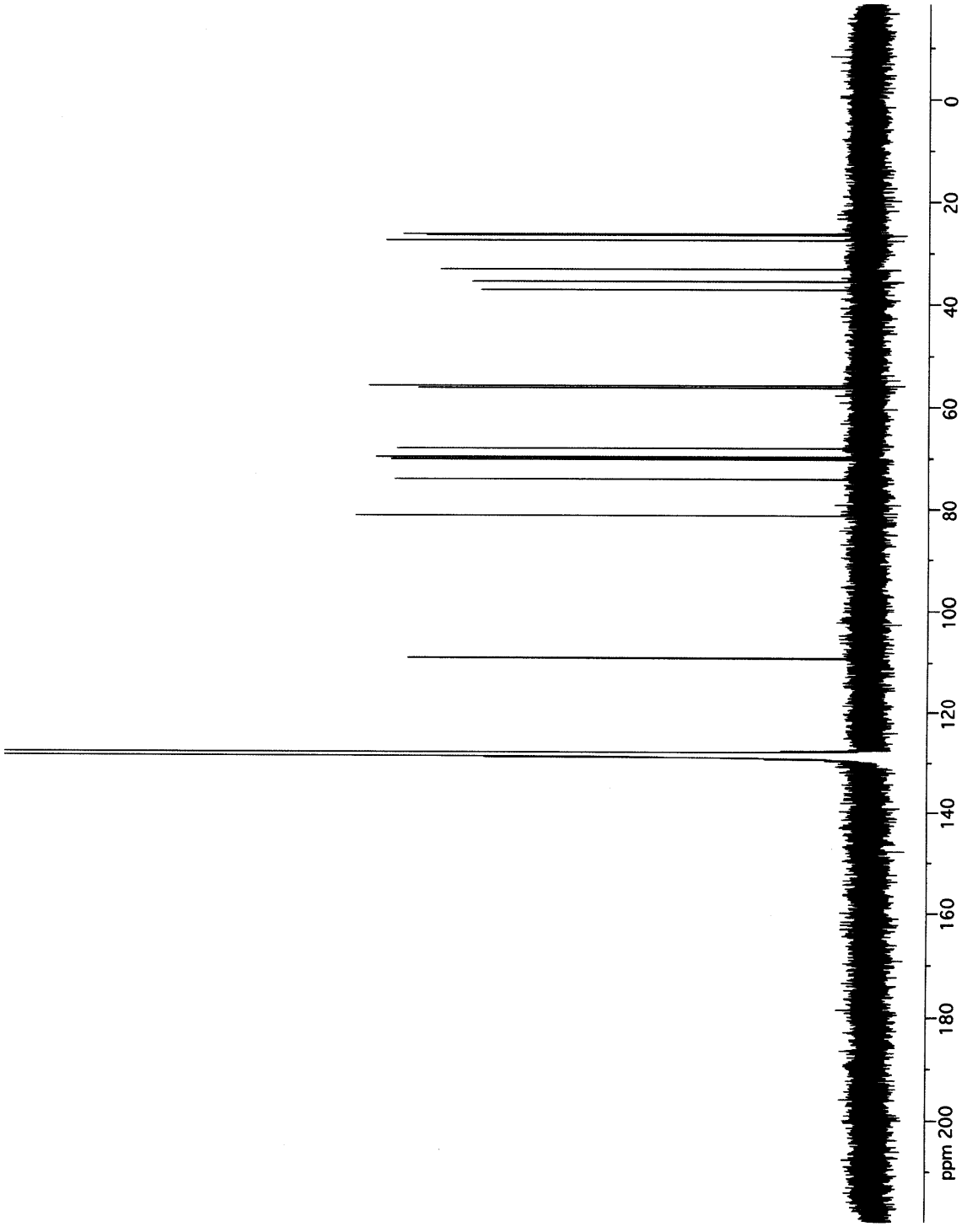

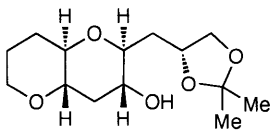

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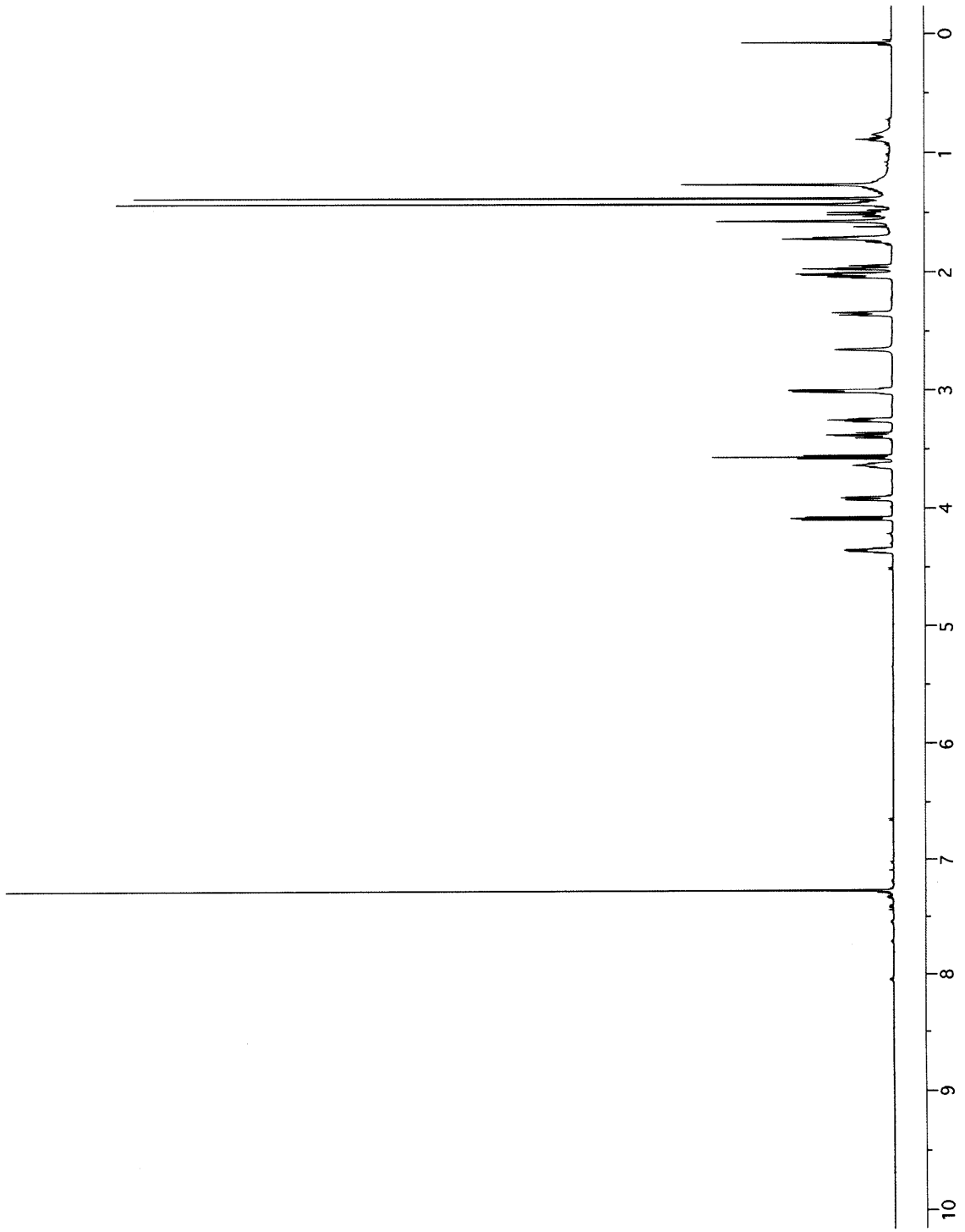

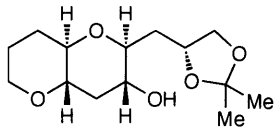
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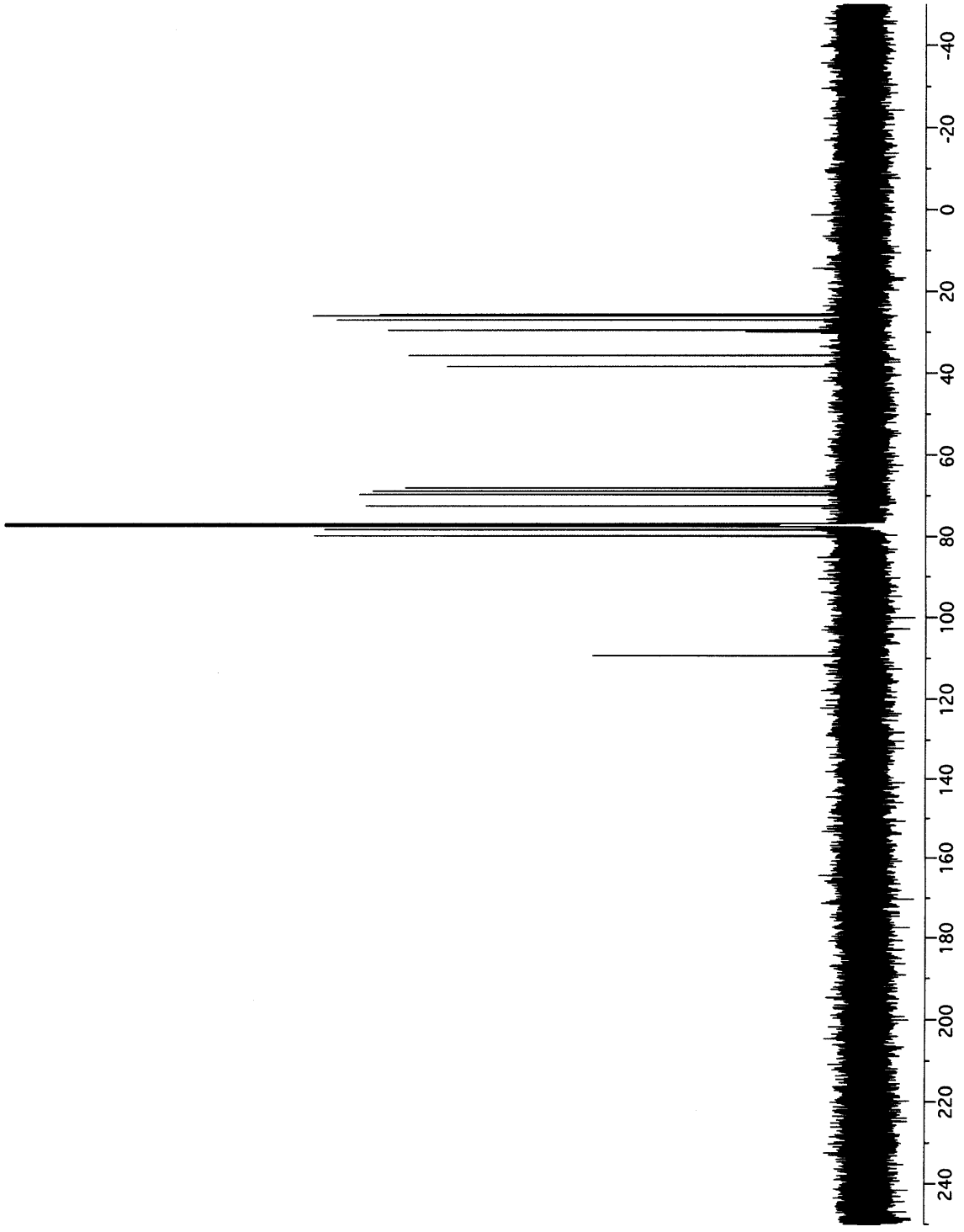
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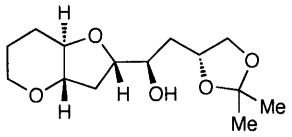

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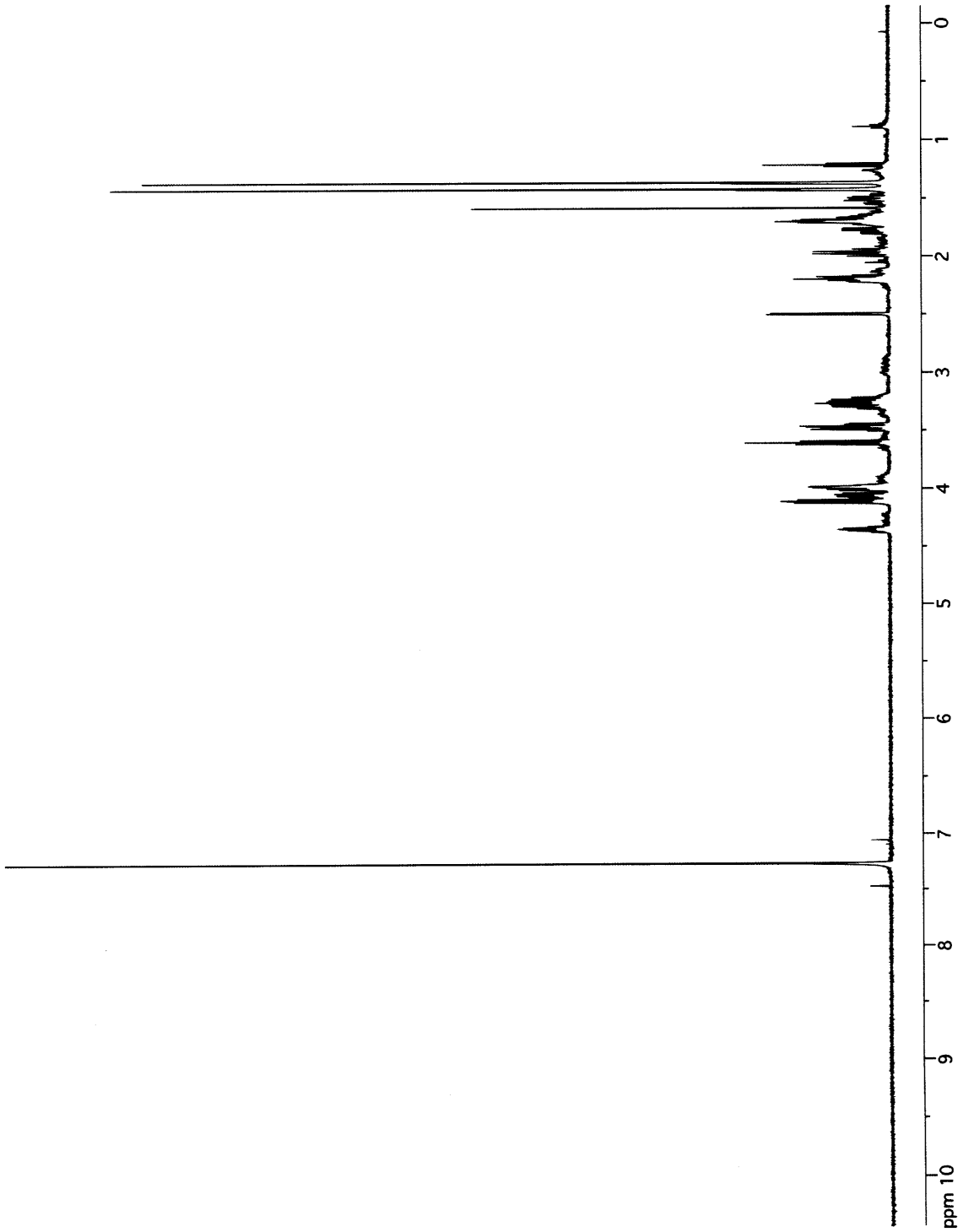

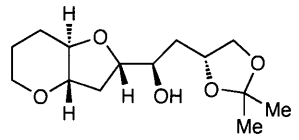
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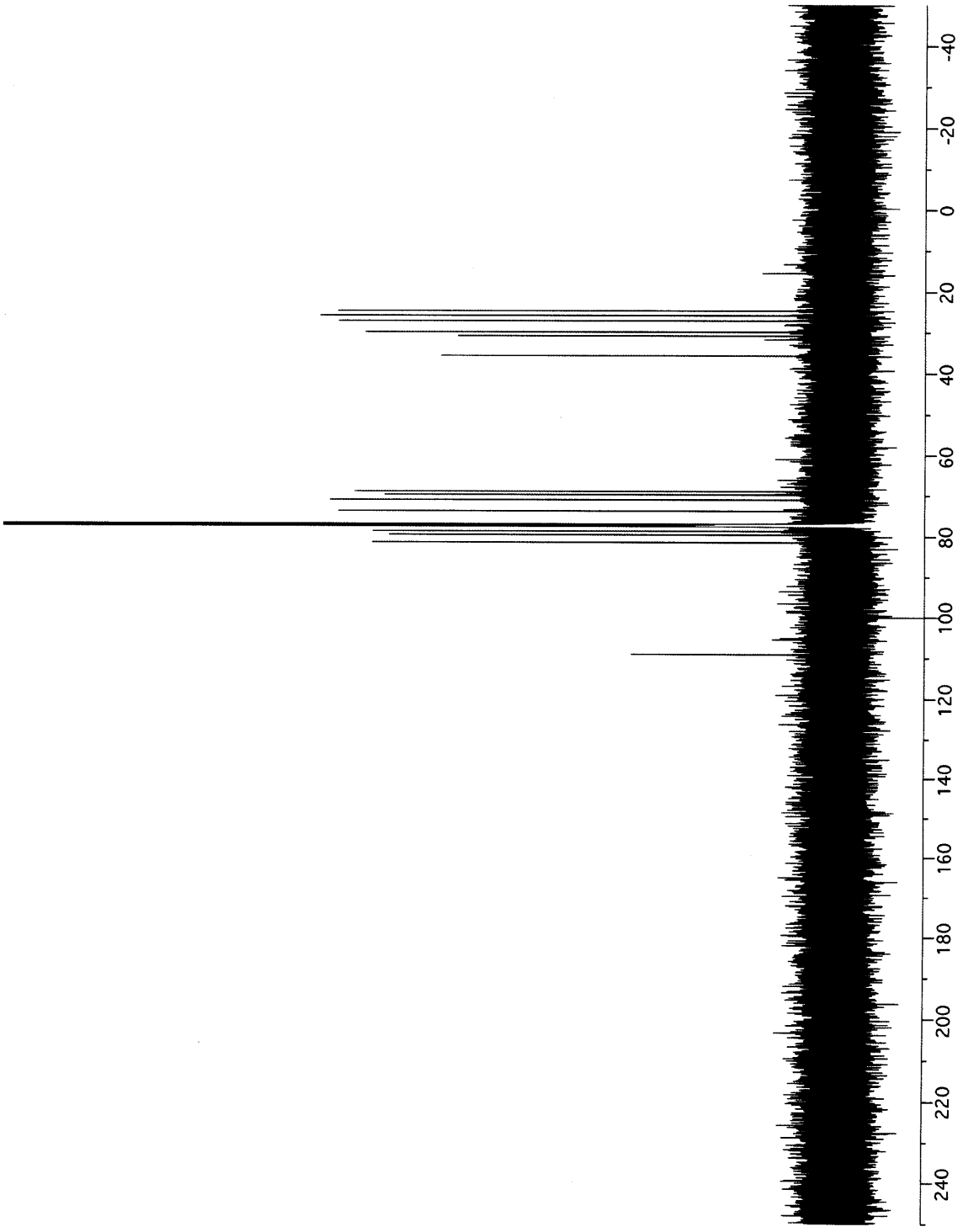
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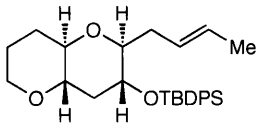

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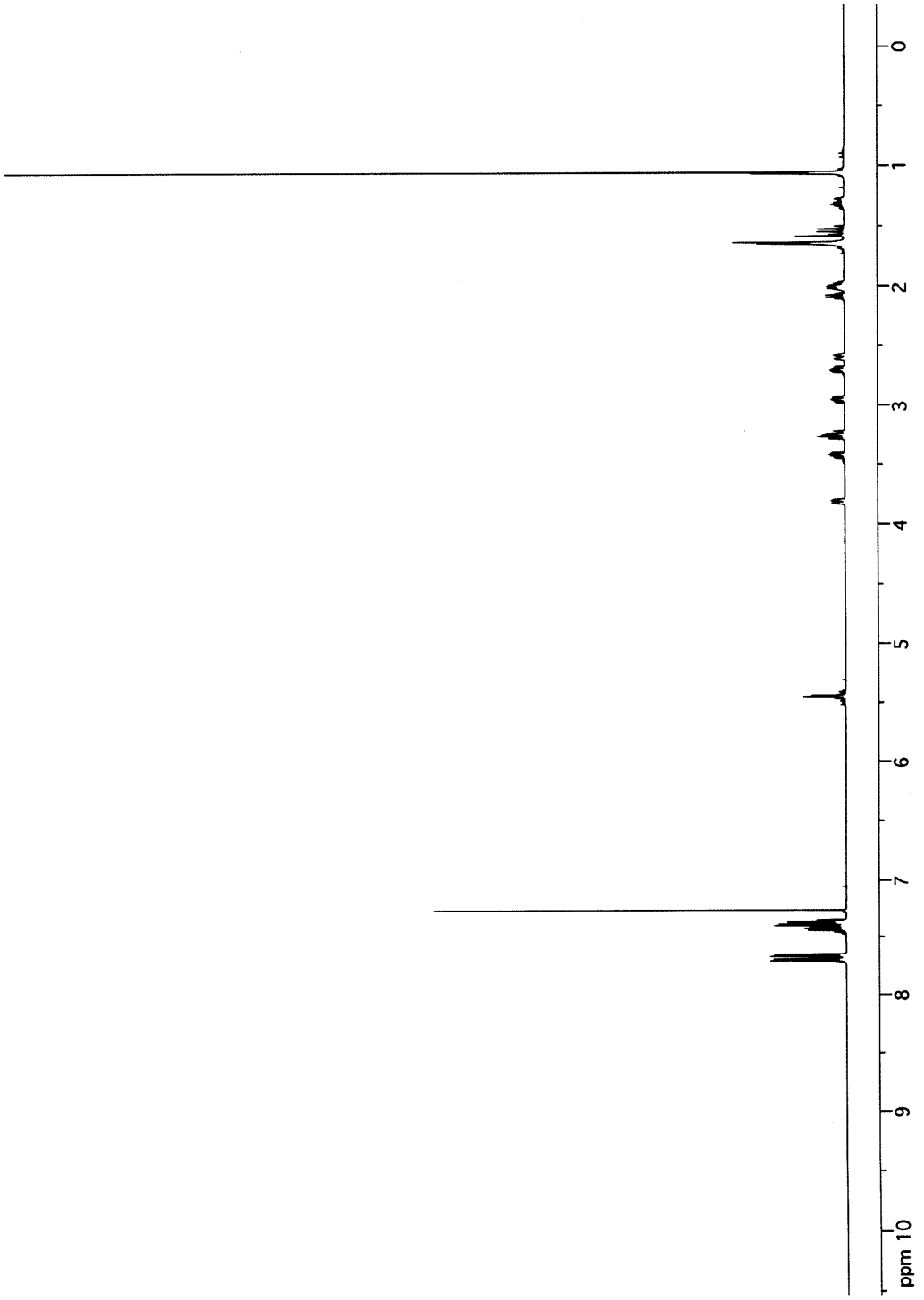

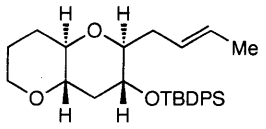
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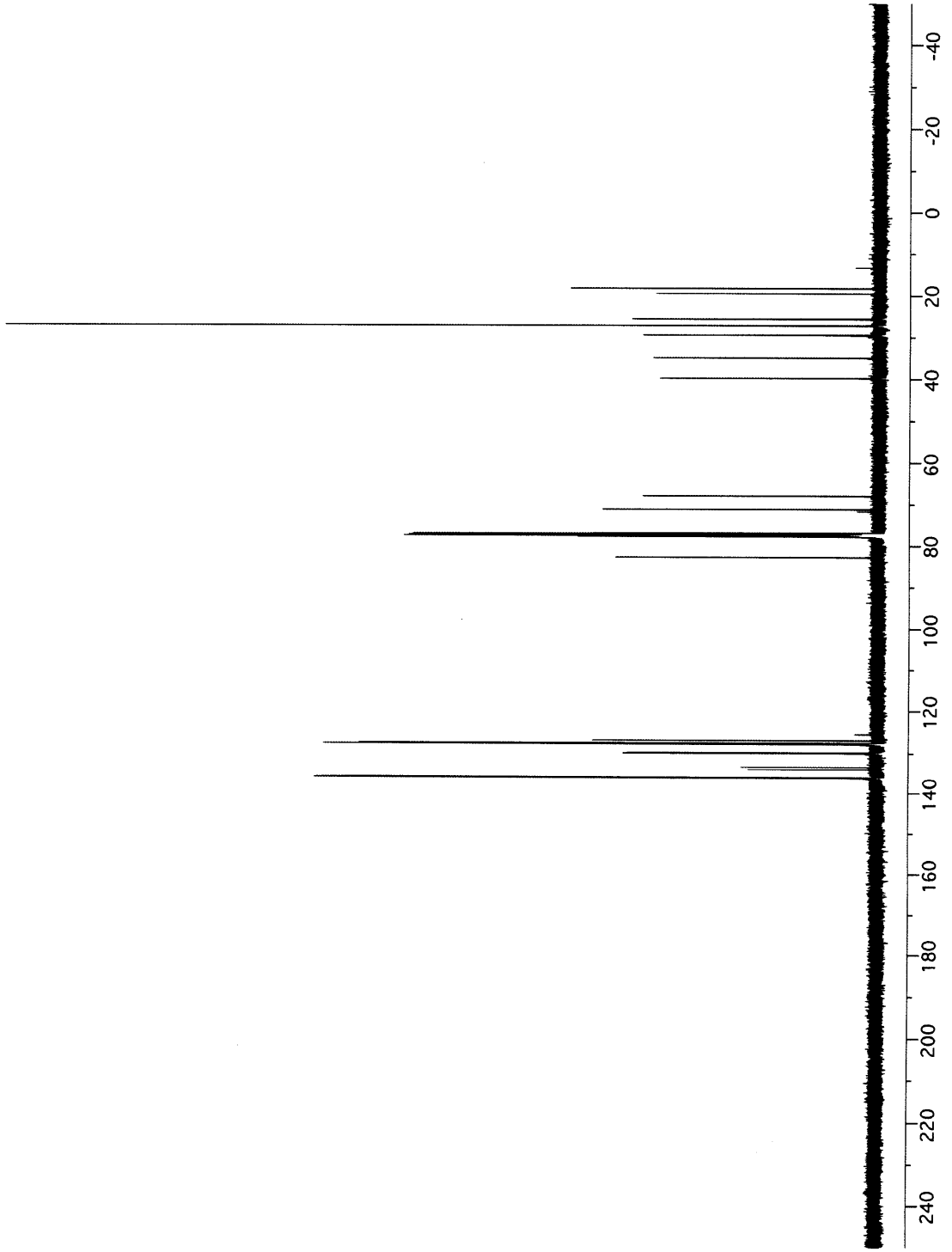
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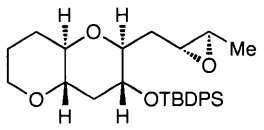

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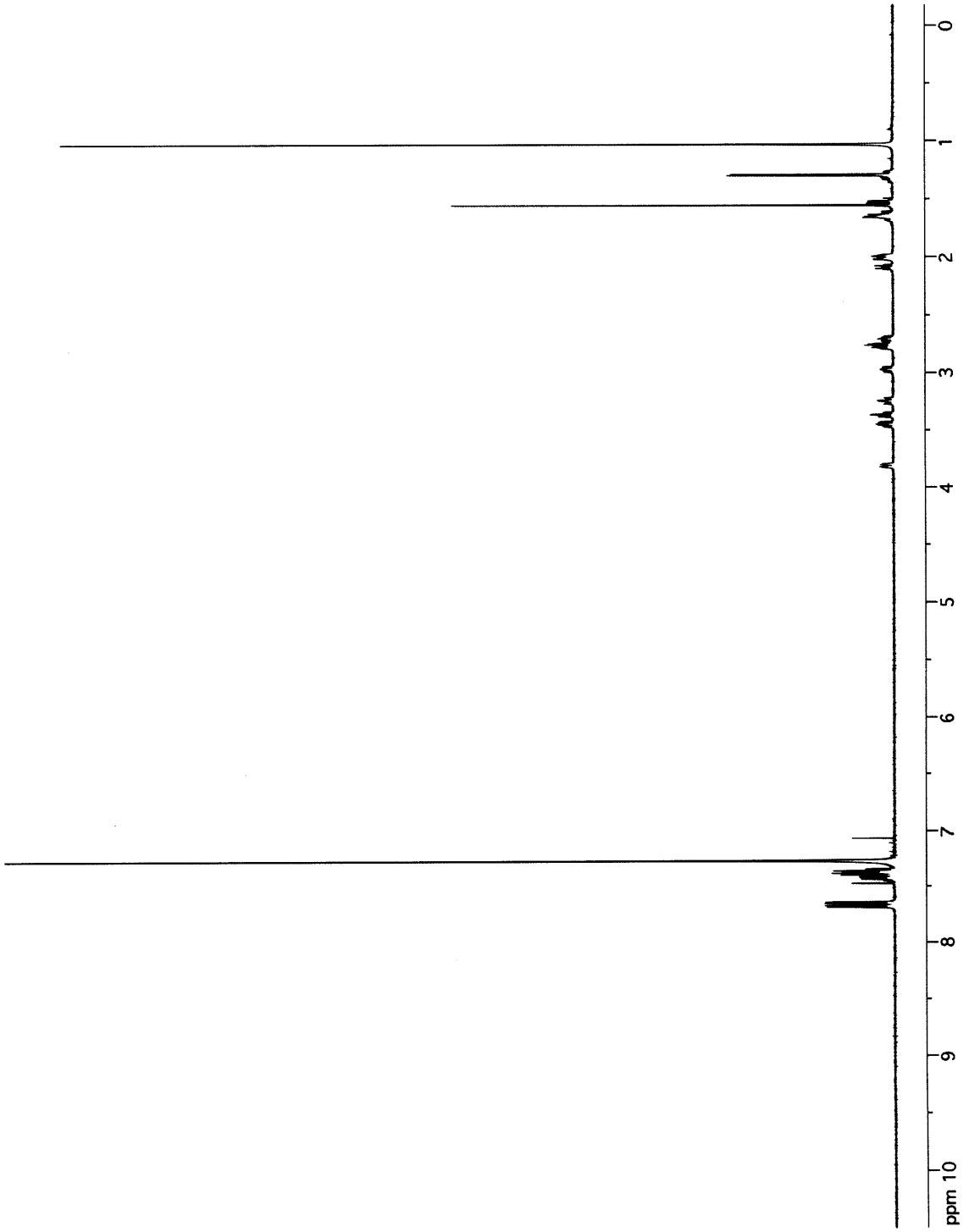

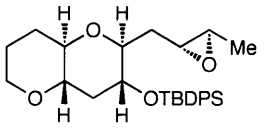
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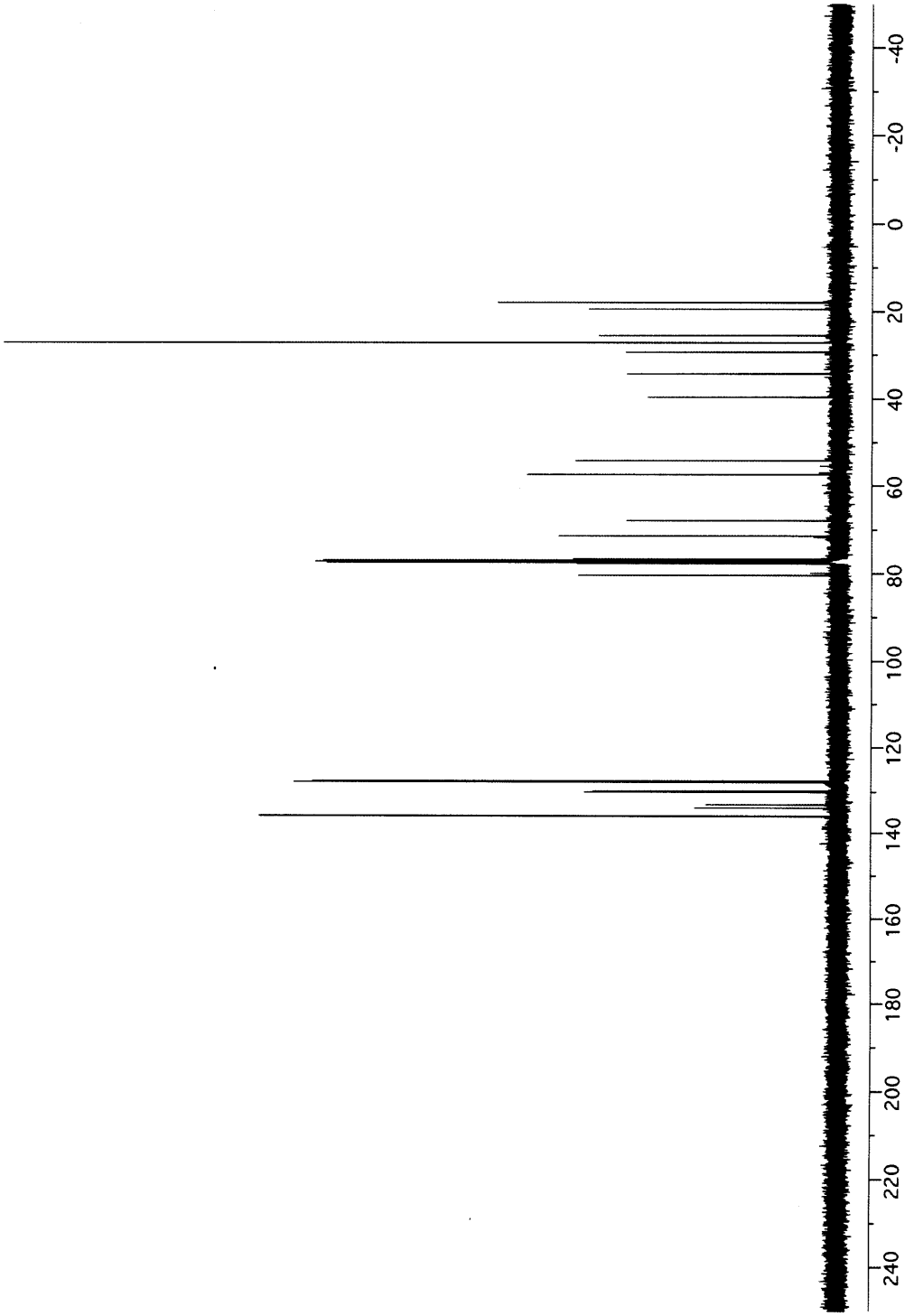
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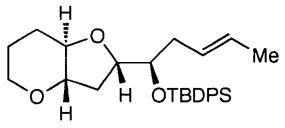

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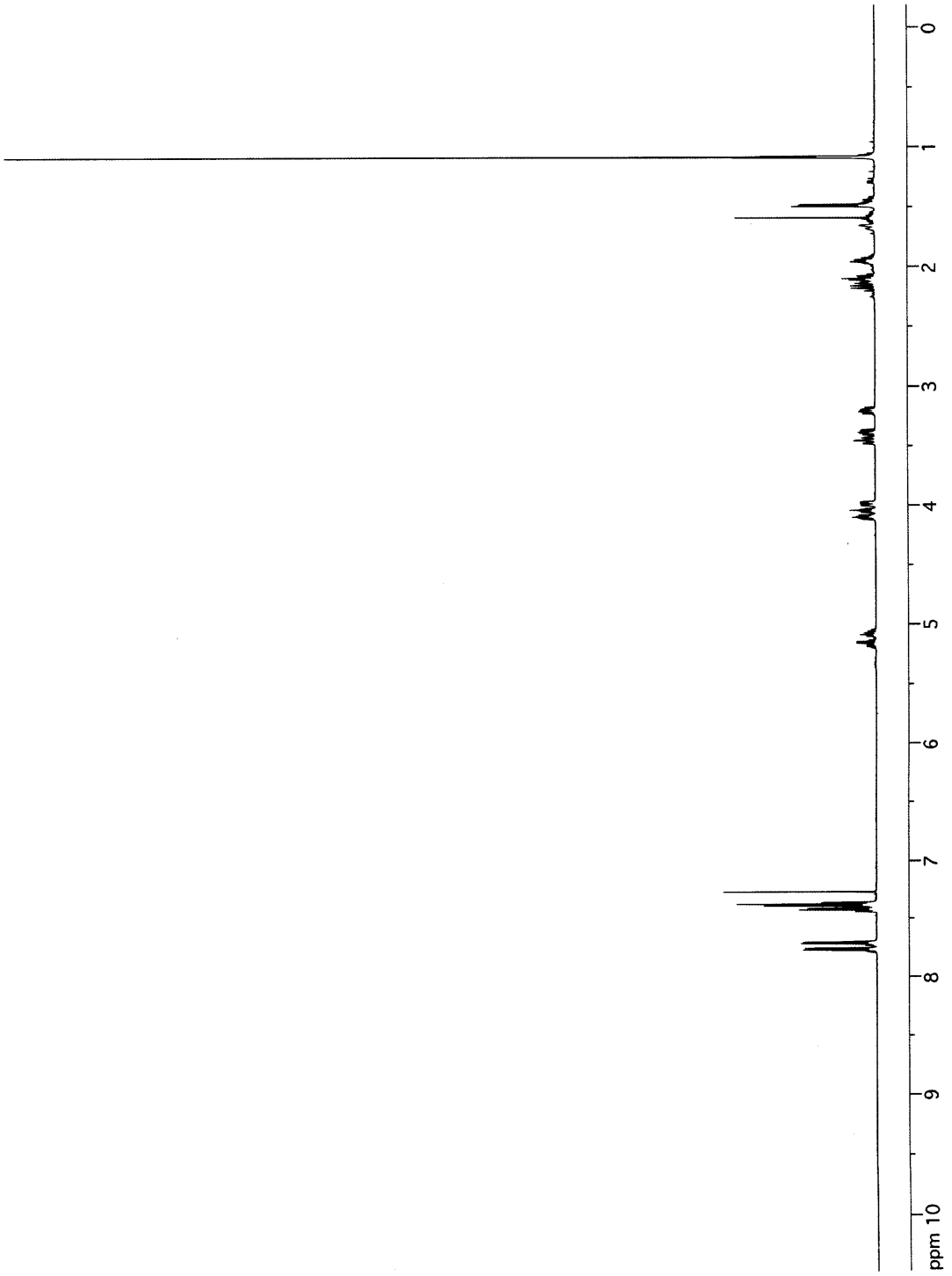

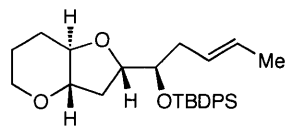

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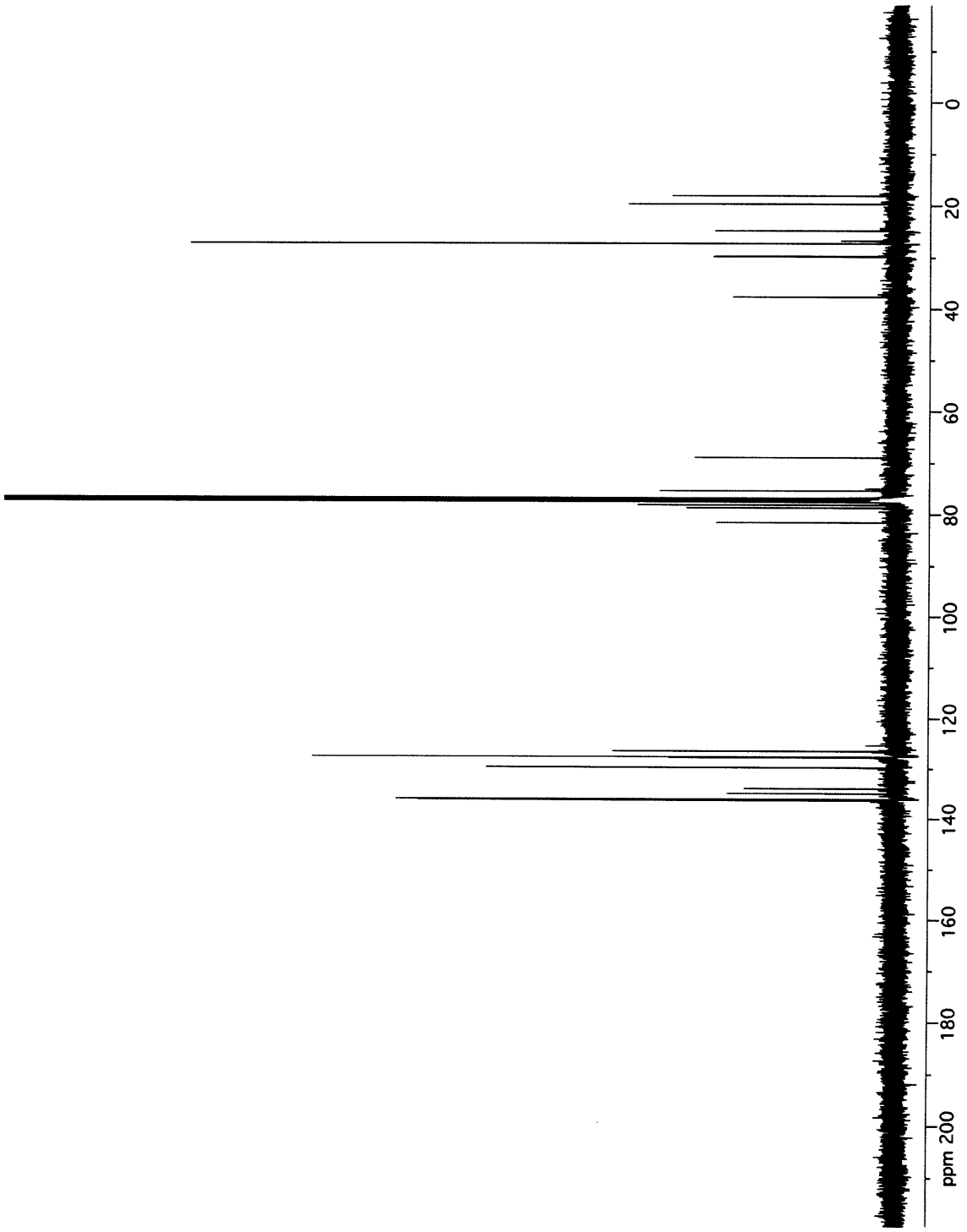

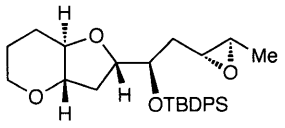

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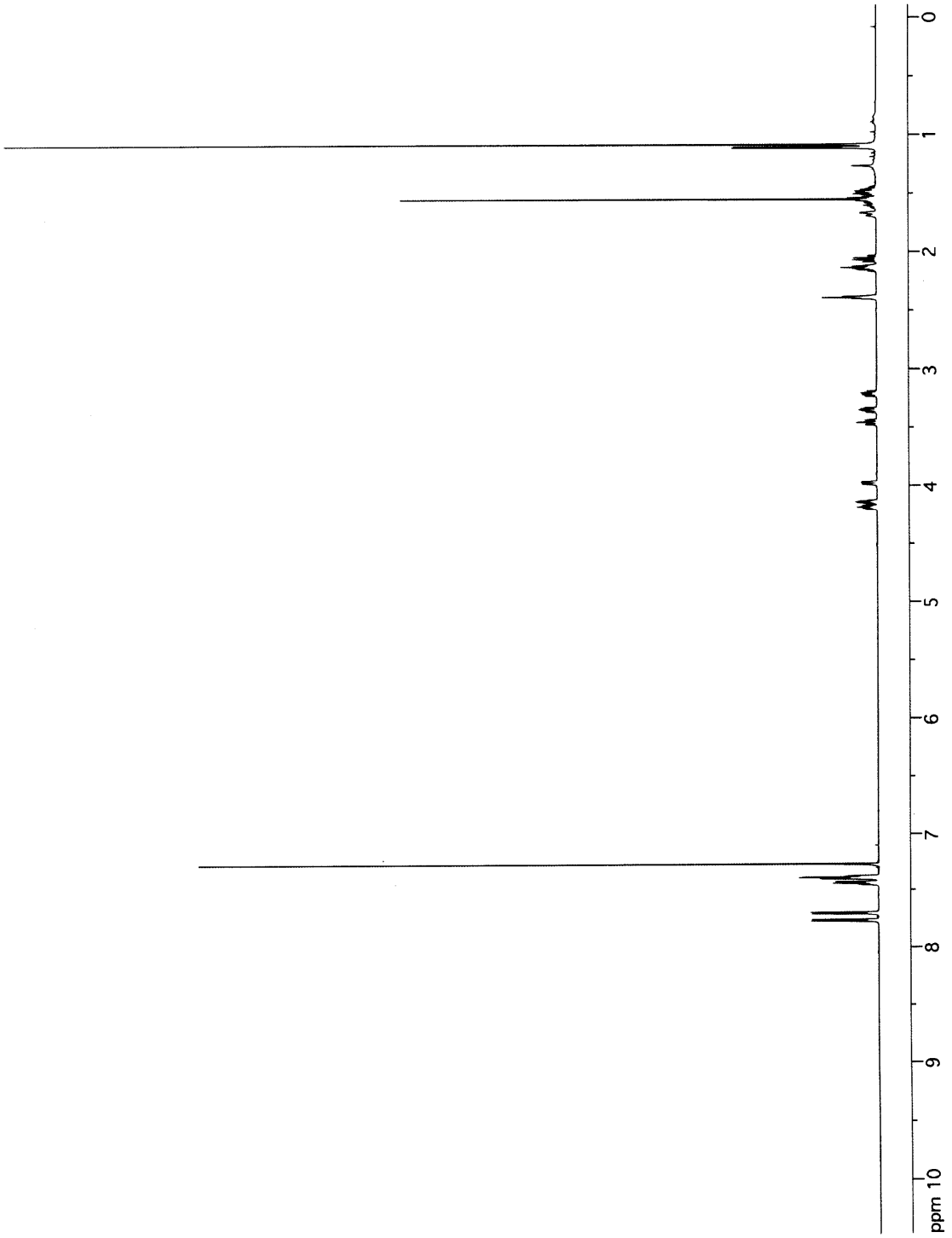

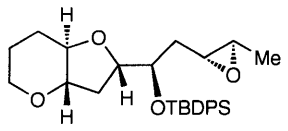
H
O
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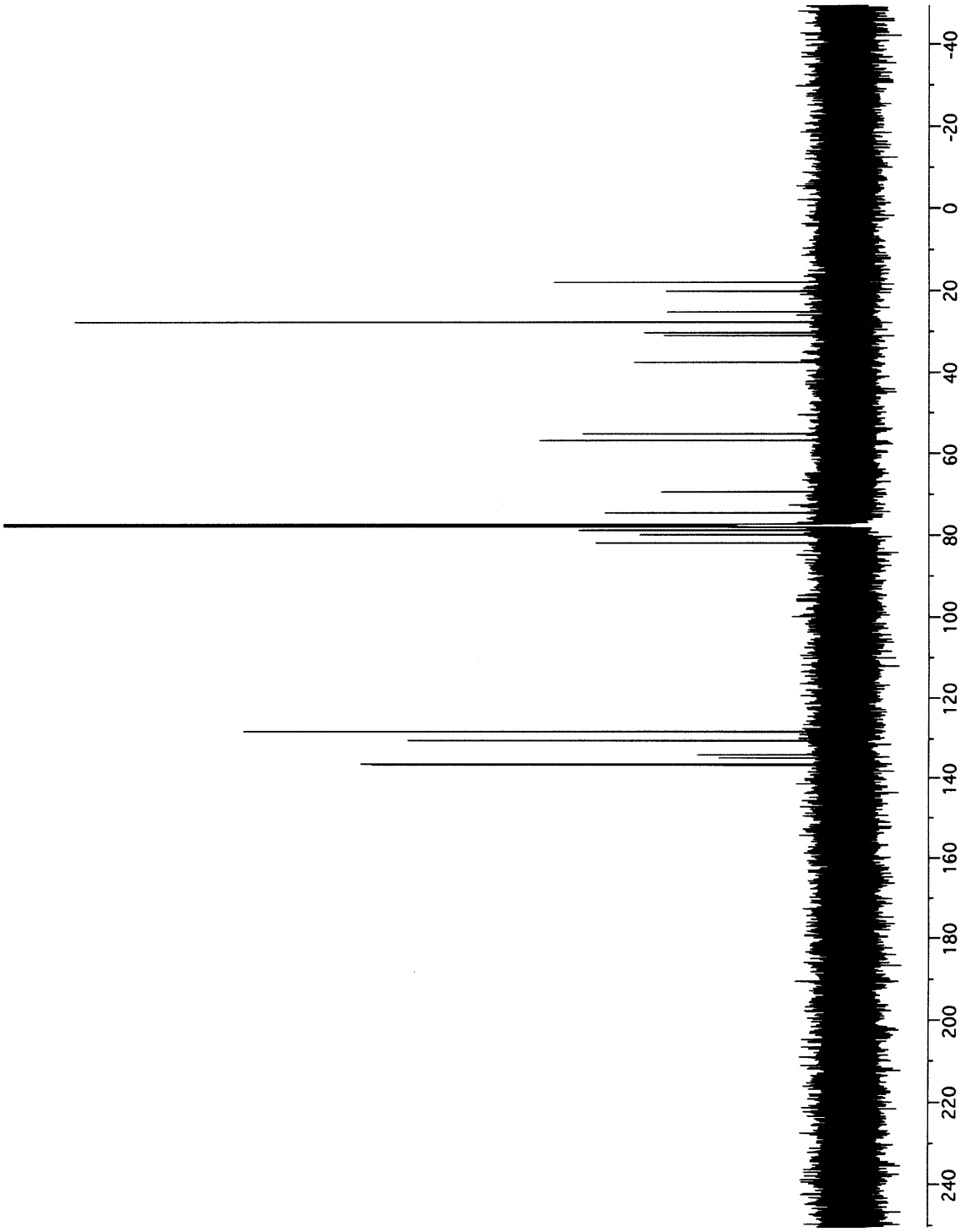
H
OTBDPS

23


-40
-20
0
20
40
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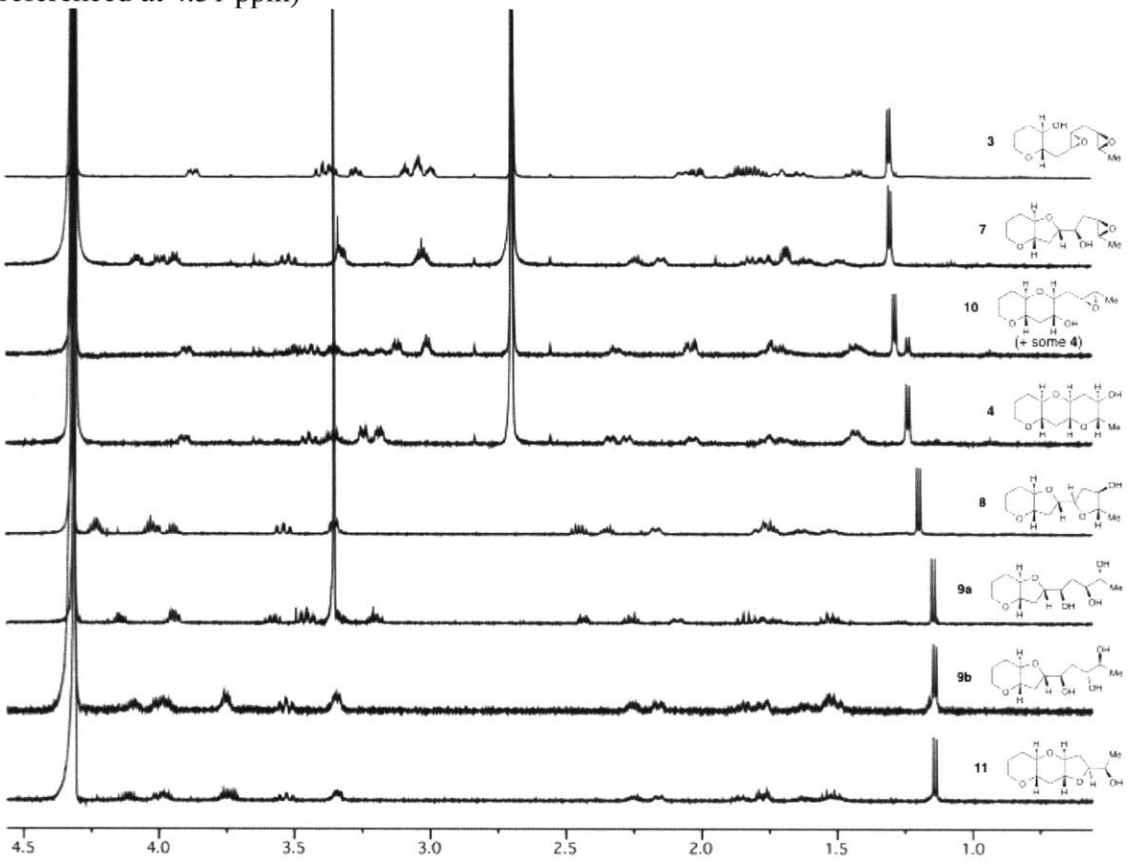
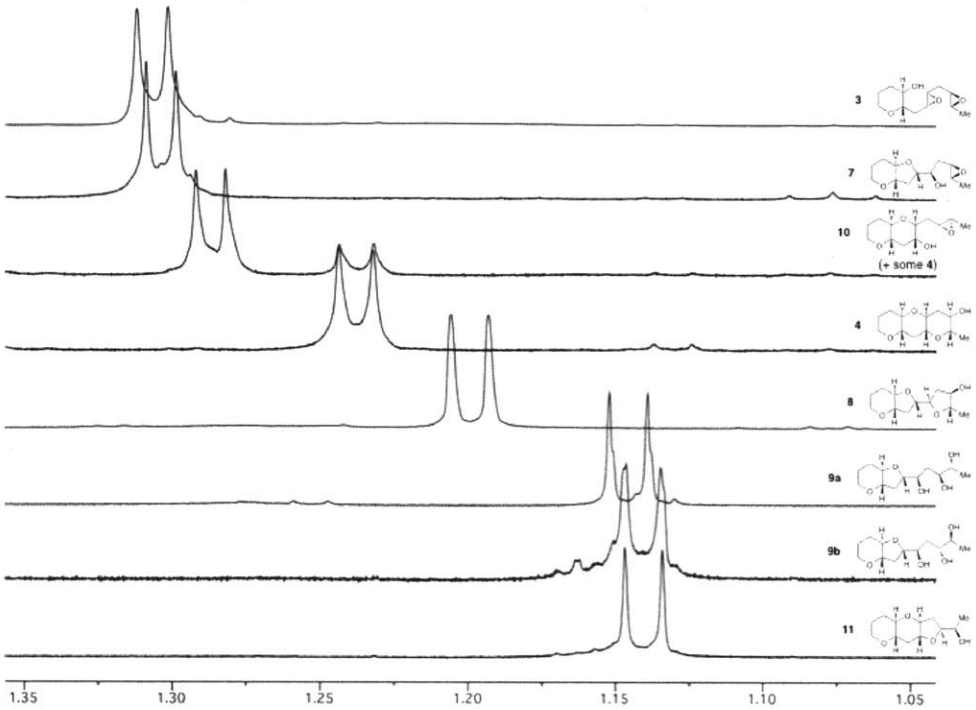
80
100
120
140
160
180
200
220
240

^{1}H spectra of compounds **3**, **4**, **7**, **8**, **9a**, **9b**, **10**, and **11** in D_2O at 70 °C (HOD peak referenced at 4.31 ppm)





Chapter IV

Preliminary Investigation of a Dioxane Template for *Endo*-Selective Epoxide-Opening Cyclization

Having shown that water-promoted *endo*-selective epoxide-opening cascades can accommodate trisubstituted epoxides, and having furthermore elucidated a stepwise mechanism for these transformations, we were eager to move beyond artificial model cascades and apply our method to the biomimetic total synthesis of a ladder polyether natural product. To date, nearly all[1] water-promoted epoxide-opening cyclizations and cascades had been templated by a simple, undecorated tetrahydropyran (THP) ring.[2] Clearly, such rings are capable templates for *endo* cyclization, and a common, integral substructure of the natural products themselves. However, in the wider context of complex molecule synthesis, unsubstituted THP rings are of limited utility, as they lack any functional group handles for further manipulation. Prior to embarking on a total synthesis, we therefore wanted to overcome this arguable limitation of our group's method. We were particularly interested in developing a "disappearing" or "detachable" template ring that might be capable of promoting *endo* cyclization and that could subsequently be cleaved to reveal handles for fragment coupling.

One such template was designed and implemented by Dr. Aaron R. Van Dyke of the Jamison group. In the course of the synthesis of the *HIJK* ring system of gymnocin A, Van Dyke and Jamison developed a synthetically versatile acetal or 1,3-dioxane template for *endo*-selective epoxide-opening cyclization (Scheme 1). Upon cyclization of epoxy alcohol **1**, THP **2** is formed. The benzylidene acetal can be cleaved to liberate a 1,3-diol (**3**), which can then be manipulated further.

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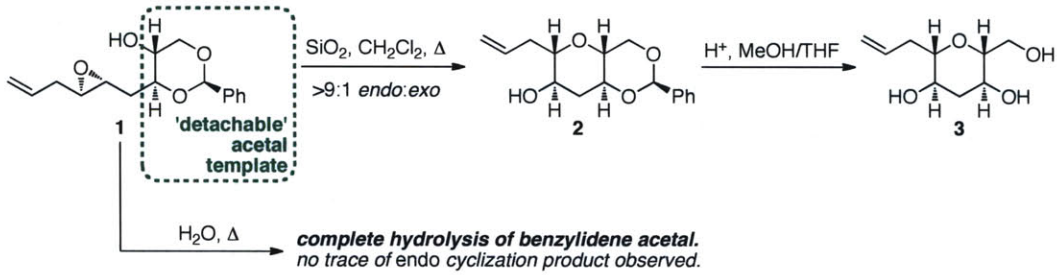
[1] The exception is a densely substituted THP ring used as template in a cascade of three epoxide openings en route to the *HIJK* ring system of gymnocin A; see: Van Dyke, A. R.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 4430.

[2] (a) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189. (b) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383. (c) Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678. (d) Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, *38*, 3175.

Scheme 1. Benzylidene acetal template for *endo*-selective epoxide-opening cyclization. (Van Dyke and Jamison, ref. 1 and 3)



Unfortunately, this system did not lend itself to the study of cascade reactions in water. The benzylidene acetal of **1** proved insufficiently robust to survive the extended heating in water required to achieve epoxide opening. The template of **1** was cleaved faster than cyclization could occur (Scheme 1). Instead of water, silica gel (SiO_2, or its monomeric form, silicic acid) in dichloromethane was found to be the best promoter.[1,3] In this reaction, silica may be acting as a simple mild Brønsted acid or perhaps as a "bifunctional" catalyst like neutral water, as SiO_2 can serve as both a hydrogen bond donor and acceptor.[4]

To enable the use of a detachable acetal template in water-promoted epoxide-opening cascades, the logical solution was naturally to move to a less labile acetal. We were drawn to methylene acetal templated epoxy alcohol **4** for two reasons (Figure 1). First, it is the acetal most resistant to hydrolysis. Second, we hoped that cyclizations of **4** might shed some light on the mechanism of water-promoted epoxy alcohol cyclization. As a methylene acetal lacks any potential complicating conformational effects that could arise from a substituent at the 2 position, we predicted it would be most directly comparable to the parent THP template.

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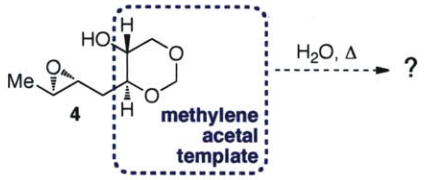
[3] Van Dyke, A. R. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 2009.

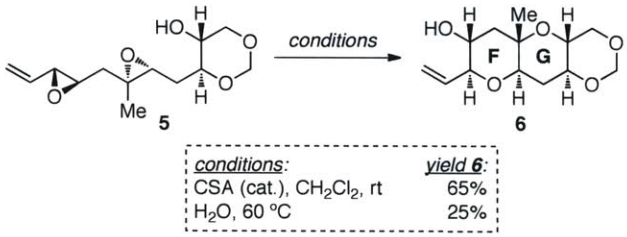
[4] (a) Iler, R. K. *The Chemistry of Silica*; Wiley: New York, 1979. (b) Kobayashi, T.; DiVerdi, J. A.; Maciel, G. E. *J. Phys. Chem. C* **2008**, *112*, 4315., and references therein.

Figure 1. Epoxy alcohol templated by a methylene acetal.



A successful *endo*-selective epoxide-cascade templated by a methylene acetal was demonstrated by Dr. Van Dyke. Diepoxy alcohol **5** cyclized to provide tricycle **6**, which maps onto the *FG* ring system of the ladder polyether gambierol (Scheme 2).[3] While the yield of **6** from reaction in water was low, this experiment demonstrated that the methylene acetal would survive extended heating in water and was a viable template.

Scheme 2. Cascade to the *FG* ring system of gambierol templated by a methylene acetal. (Van Dyke and Jamison, ref. 3)

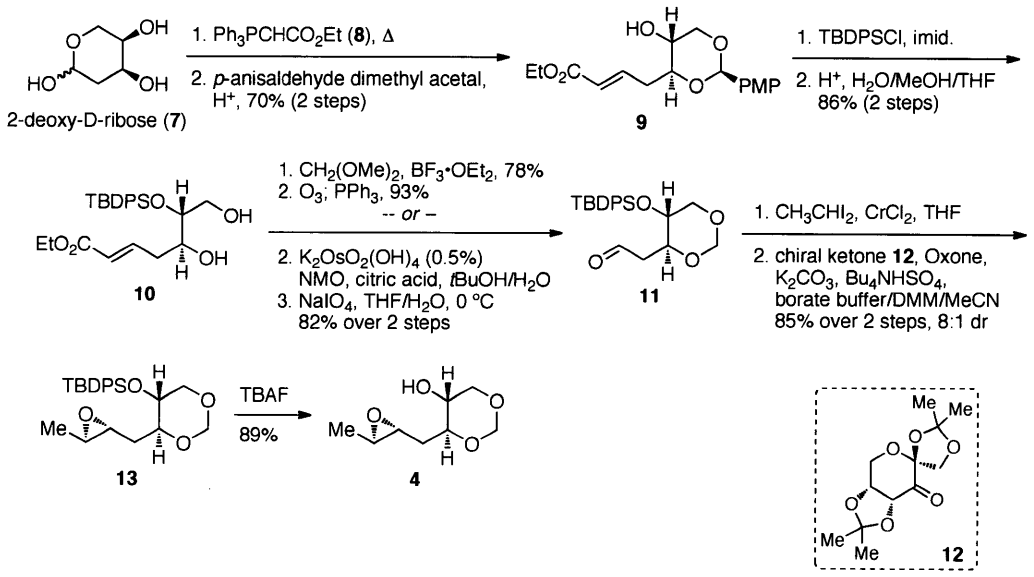


Wishing to learn more about the fundamental reactivity of this water-stable 1,3-dioxane template, we subsequently set out to prepare simplified epoxy alcohol **4**. We used a mild variation on a well-precedented synthetic sequence that has been used by Nicolaou,[5] Sasaki and Tachibana,[6] and Inoue[7] for the synthesis of ladder polyethers. Synthesis commenced with Wittig olefination of 2-deoxy-D-ribose[8] (**7**), an inexpensive chiral pool intermediate (Scheme 3). After reaction of **7** with stabilized phosphorane **8**, the resulting 1,2,3-triol was derivatized to the PMP acetal under conditions selective for 1,3-protection. The free secondary alcohol of **9** was then protected as its TBDPS ether, and the PMP acetal was hydrolyzed to afford diol **10**. After installation of the methylene

[5] Nicolaou, K. C.; Nugiel, D. A.; Couladouros, C.; Hwang, C. K. *Tetrahedron* **1990**, *46*, 4517.
[6] Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019.
[7] Inoue, M.; Wang, J.; Wang, G.-X.; Ogasawara, Y.; Hirama, M. *Tetrahedron* **2003**, *59*, 5645.
[8] This monosaccharide is available in bulk for less than $1/g.

acetal, the enoate was ozonolyzed to afford aldehyde **11** in six steps from deoxyribose. Ozonolysis proved troublesome on large scale, with low yields presumably resulting from decomposition of the ozonide over long reaction times. Therefore, an alternative two-step procedure was also explored, involving OsO_4-catalyzed 1,2-dihydroxylation[9] followed by oxidative cleavage with $NaIO_4$. Aldehyde **11** was transformed to epoxide **13** upon Takai olefination[10] with 1,1-diiodoethane and subsequent Shi asymmetric epoxidation.[11] Finally, cleavage of the silyl ether of **13** with TBAF gave epoxy alcohol **4**.

Scheme 3. Synthesis of epoxy alcohol **4**.



Dioxane-templated epoxy alcohol **4** was cyclized under our standard set of cyclization promoters (Table 1). The differences between **4** and its THP-templated congener **16**[2a,b] (Figure 2) were immediately clear. In line with the behavior of benzylidene acetal-templated **1**,[1,3] epoxy alcohol **4** cyclized with high *endo* selectivity upon activation with acids CSA, BF_3, and SiO_2 in CH_2Cl_2 (entries 1-3). Again consistent with **1**,[3] epoxy alcohol **4** also cyclized with moderate 5:1 *endo* selectivity upon activation

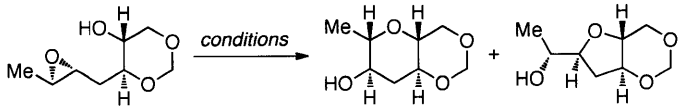
[9] The addition of citric acid improves conversion in the Os-cat. dihydroxylation of electron-poor olefins like enoates; see: Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421.

[10] Okazoe, T.; Takai, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 951.

[11] (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

with Cs_2CO_3 (entry 4). This is in marked contrast to THP-templated **16**, which cyclizes with *exo* or very low *endo* selectivity under acidic and basic activation.[2a]

Table 1. Cyclizations of dioxane-templated epoxy alcohol **4**.

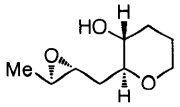


4 (>20:1 dr) **14** **15**

entry	*conditions* [a]	T (°C)	*t*	**14:15** [b]
1	(+/-)-CSA (1 equiv), CH_2Cl_2	rt	15 h	7.1:1
2	BF_3•OEt_2 (25 mol%), CH_2Cl_2	-78 to rt	30 min	>20:1
3	SiO_2 (90 mg/mg SM), CH_2Cl_2	rt	11 d	17:1
4	Cs_2CO_3 (30 equiv), MeOH	rt	40 h	5.4:1
5	deionized H_2O	rt	60 d	28:1
6	0.1 M KP_i buffer, pH 2.0	rt	60 d	17:1
7	0.1 M KP_i buffer, pH 3.0	rt	60 d	15:1
8	0.1 M KP_i buffer, pH 4.0	rt	60 d	>20:1
9	0.1 M KP_i buffer, pH 5.0	rt	60 d	>20:1
10	0.1 M KP_i buffer, pH 6.0	rt	60 d	>20:1
11	0.1 M KP_i buffer, pH 7.0	rt	60 d	>20:1
12	0.1 M KP_i buffer, pH 8.0	rt	60 d	>20:1
13	0.1 M KP_i buffer, pH 9.0	rt	60 d	9.5:1
14	0.1 M KP_i buffer, pH 10.0	rt	60 d	7.4:1
15	0.1 M KP_i buffer, pH 11.0	rt	60 d	6.4:1
16	0.1 M KP_i buffer, pH 12.0	rt	60 d	6.4:1

[a] Reactions were carried out at 0.02 M and taken to >95% conversion of **4**. [b] Determined by ^{1}H NMR.

Figure 2. THP-templated epoxy alcohol **16**.



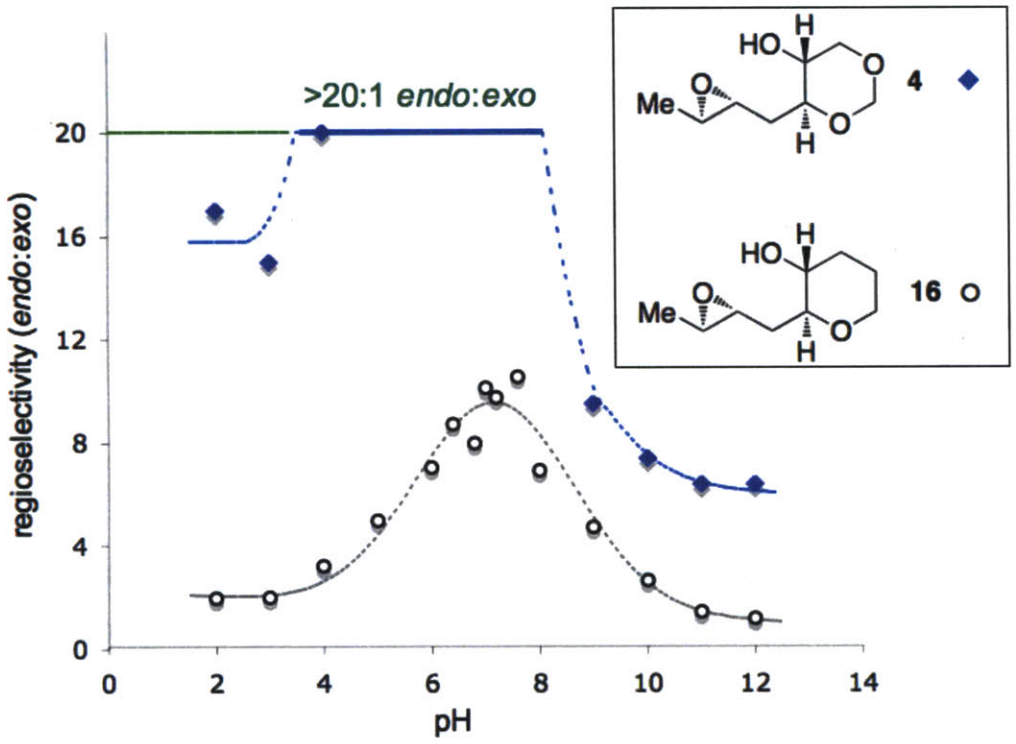
16

Cyclization in water revealed two interesting properties of epoxy alcohol **4**. First, **4** reacts slowly in neutral water. In fact, acetal **4** cyclized in D_2O at ambient temperature with a remarkably long half-life of approximately eight days, about an order of magnitude slower than THP **16**.[2b] Second, stirring **4** in deionized water induced cyclization with greater than 20:1 *endo*:*exo* selectivity.[12] This result was corroborated in

[12] The ratio **14:15** was determined by ^{1}H NMR, and so precise measurement of ratios in excess of 95:5 is questionable. However, repeated cyclization experiments of **4** in pH 7 buffer and measurement of each using an NMR spectrometer equipped with a cryoprobe all point to a ratio **14:15** of >50:1.

KP_i buffer (Table 1, entries 6-16, and Figure 3). Cyclization of **4** in acidic water (pH 2-4, entries 6-8) proceeded with high *endo* selectivity of 15:1 or better, consistent with what was observed upon activation by acid in organic solvents. In neutral and near-neutral water (pH 5-8, entries 9-12), **4** cyclized with >20:1 regioselectivity. On adjusting the reaction medium to increasingly basic pH (pH 9-12, entries 13-16), regioselectivity declined to a minimum of 6.4:1 at pH 11 and 12. Thus the overall trend in cyclizations of epoxy alcohol **4** is peak regioselectivity near neutral pH and lower regioselectivity in acidic and basic solution. This mirrors the trend observed for THP-templated epoxy alcohol **16**, although *endo* selectivity was much higher in cyclizations of acetal **4** at all pH values tested (Figure 3).

Figure 3. Dependence of regioselectivity on pH in cyclizations of **4** and **16**[2a] (room temperature, 0.1 or 1.0 M KP_i buffer).

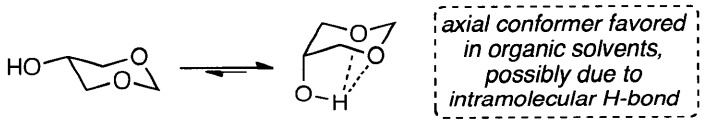


Methylene acetal-templated epoxy alcohol **4** cyclized with good-to-excellent regioselectivity under every condition examined. Thus the 1,3-dioxane seems to be a

uniquely powerful template, effecting 6-*endo* opening of a "directing group-free" *trans*-disubstituted epoxide under activation by acid, base, and neutral water. We cannot completely rationalize the differences between THP-templated **16** and dioxane-templated **4**. To explain the lower reaction rate of **4** in water, at least part of the disparity may be attributable to the inductive electron-withdrawing effect of the additional oxygen atom in the ring, which should make the templated alcohol less nucleophilic. Inductive withdrawing effects on the epoxide have also been invoked to rationalize trends in regioselectivity (see Chapters II and III), but in this case O_1 of the dioxane ring would seem to be too distant to exert any meaningful influence on the epoxide.

It is plausible that cyclization of **4** is slower for conformational reasons, and it is perhaps likely that cyclization of **4** is highly *endo* selective for the same reasons. One factor affecting rate could be a lower equilibrium population of reactive conformers of **4**; the ground state of 5-hydroxy-1,3-dioxanes in organic solvent is known to be the conformation in which the hydroxyl substituent is axial and possibly engaged in an intramolecular hydrogen bond with the ring oxygens (Figure 4).[13] Epoxy alcohol **4** may thus be locked in an unproductive diaxial conformation. However, this internal hydrogen bond may be broken completely by water and therefore irrelevant.

Figure 4. Conformational equilibrium of 5-hydroxy-1,3-dioxane in organic solvent (ref. 13).



In chair conformations, 1,3-dioxanes are also "flattened" along the C_4–C_5–C_6 bonds, relative to cyclohexane and THP rings.[14] The shorter C–O bond distance as compared to C–C causes the C_4–C_5–C_6 plane to be closer to coplanar with the C_4–O_3 and C_6–O_1 bonds. This should increase the distance between epoxide and alcohol reactive partners in the coequatorial chair conformer of **4** and thereby suppress reaction from this

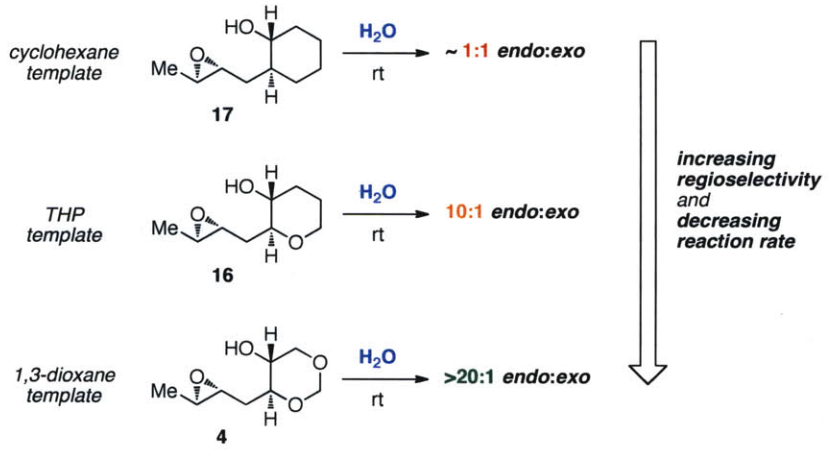
[13] (a) Baggett, N.; Brimacombe, J. S.; Foster, A. B.; Stacey, M.; Whiffen, D. H. *J. Chem. Soc.* **1960**, 2574 (b) Baggett, N.; Bukhari, M. A.; Foster, A. B.; Lehmann, L.; Webber, J. M. *J. Chem. Soc.* **1963**, 4157. (c) Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1.

[14] Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444.

conformer. Such an effect would be beneficial if, indeed, cyclization from the chair conformer is unselective and *endo*-selective cyclization instead occurs through a twist-boat or other higher energy conformation.[2b] Flattening of the dioxane ring likely also perturbs the dihedral angle between the hydroxyl oxygen and the methylene carbon of the epoxide substituent in boat and twist boat conformers. The trajectory of approach between alcohol in epoxide would be altered correspondingly, which would in turn impact the regioselectivity of epoxide opening.[15] Of course, the incorporation of a second Lewis basic oxygen atom into the template may also simply alter the network of hydrogen bonds around the epoxy alcohol, with unpredictable but apparently beneficial effects on regioselectivity.

A great deal of mechanistic study remains to be done. We conclude with the observation of an evident trend of improving *endo* selectivity with increasing oxygenation of the template ring (Scheme 4). The potential Achilles heel of the 1,3-dioxane template is slow cyclization. However, in the following chapter we demonstrate the success of a cascade of three *endo* epoxide openings templated by a 1,3-dioxane. The use of a 1,3-dioxane template in the context of total synthesis is further advantageous, as the unit can be cleaved and functionalized after completion of the cascade.

Scheme 4. Comparison of monocyclic templates for epoxide-opening cyclization. (Results for **16** and **17** from Byers and Jamison, ref. 2b.)



[15] (a) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270. (b) Na, J.; Houk, K. N.; Shevlin, C. G.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 8453. (c) Coxon, J. M.; Thorpe, A. J. *J. Org. Chem.* **1999**, *64*, 5530.

Experimental Section

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Reactions were magnetically stirred unless otherwise stated. All temperatures are reported in °C.

Dichloromethane, tetrahydrofuran (THF), Et_2O, and triethylamine were purified via an SG Water USA solvent column system. Reactions in water used deionized water without further purification.

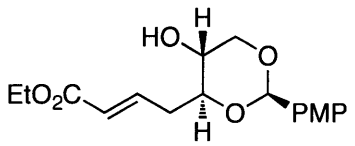
Cs_2CO_3 was oven-dried overnight before use. Chiral ketone **12**, used in Shi asymmetric epoxidation was prepared from D-fructose according to the procedure of Vidal-Ferran and coworkers.[16]

All other reagents and solvents were used as obtained, without further purification.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ceric ammonium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). Analytical HPLC was performed on the column phase indicated on a Hewlett-Packard 1100 Series HPLC. Preparative HPLC was performed on the column phase indicated on an Agilent 1200 Series HPLC.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Varian Inova-500 MHz spectrometer, a Bruker AVANCE-400 MHz spectrometer, or a Bruker AVANCE-600 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual $CHCl_3$ in $CDCl_3$ (7.27 ppm) or C_6HD_5 in C_6H_6 (7.15 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and app = apparent), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm) or C_6D_6 (128.6 ppm), on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR. High Resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Jasco Model 1010 polarimeter at 589 nm.

[16] Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143-10146.



9

PMP acetal 9: To a slurry of 2-deoxyribose (42.0 g, 313 mmol) in THF (625 mL) was added (carbethoxymethylene)triphenylphosphorane ($Ph_3P{=}CHCO_2Et$, 120 g, 344 mmol). This mixture was heated to vigorous reflux for 3 h. Upon heating the solution became a homogenous golden yellow. The reaction was then cooled to rt and concentrated *in vacuo* to afford the crude enoate as a heavy, orange-brown oil, which was carried on into PMP acetal protection without further purification.

This crude diol was dissolved in CH_2Cl_2 (500 mL), to which was added first *p*-anisaldehyde dimethyl acetal (96 mL, 103 g, 563 mmol) and then (+/-)-camphorsulfonic acid (14.5 g, 63 mmol). Upon addition of CSA, the reaction solution immediately turned paler, becoming a light orange-brown. After stirring 14 at rt, the reaction was quenched with Et_3N (11.8 mL, 8.6 g, 84.5 mmol) and subsequently concentrated *in vacuo* to a heavy red oil. This was purified by column chromatography (gradient 30% to 50% to 100% EtOAc in hexanes) to afford PMP acetal **9** as a yellow oil (73 g, 220 mmol, 70%) contaminated with an additional quantity of triphenylphosphine oxide, which does not adversely affect the next step. R_f of **9** = 0.46 (50% EtOAc in hexanes). Repurification of a small quantity of this material by the same conditions gave **9** in >95% purity:

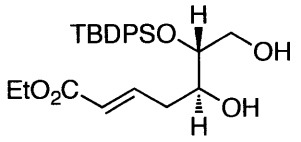
$[\alpha]^{22}_D$ = -26.1 (*c* = 1.23, $CDCl_3$).

IR (thin film, NaCl) 3462, 2979, 2935, 1716, 1655, 1615, 1519, 1251, 1174, 1080, 1034 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.08 (dt, *J* = 15.7, 7.2 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.96 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.44 (s, 1H), 4.24 (dd, *J* = 10.2, 4.2 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.72-3.53 (m, 3H), 2.80 (dddd, *J* = 15.1, 6.9, 3.2, 1.6 Hz, 1H), 2.56 (app dtd, *J* = 15.1, 7.5, 1.4 Hz, 1H), 2.19 (d, *J* = 5.2 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 160.2, 144.8, 130.2, 127.6, 123.9, 113.8, 101.1, 80.5, 71.4, 65.5, 60.6, 55.5, 34.8, 14.4.

HR-MS (ESI) *m/z* calcd for $C_{17}H_{22}O_6$ $[M+H]^+$: 323.1489, found 323.1482.



10

Diol 10: To a solution of alcohol **9** (17.6 g, 53 mmol) in DMF (25 mL) was added first imidazole (5.4 g, 80 mmol) and then TBDPSCl (16.3 mL, 17.5 g, 64 mmol). The resulting viscous solution was stirred at rt for 16 h., then quenched by addition of sat. $NH_4Cl_{(aq)}$ (~50 mL). The aqueous layer was separated and extracted with EtOAc (3x~150 mL) and the combined organic layers were washed with brine (~50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude silyl ether as a pale yellow oil (R_f = 0.52, 20% EtOAc in hexanes). This crude material was carried forward into acetal hydrolysis without further purification.

To a solution of one half of this crude material in a 12:3:1 v:v:v mixture of MeOH:THF:H_2O (212 mL) was added *p*-toluenesulfonic acid monohydrate (1.0 g, 5.3 mmol). The solution was heated to reflux (~70 °C on hot plate) for 2 h. At this point TLC indicated formation of the desired diol (R_f = 0.67, 50% EtOAc in hexanes) along with a trace of unreacted starting material (R_f = 0.94, 50% EtOAc in hexanes). The solution was cooled in an ice bath, quenched with Et_3N (1.1 mL, 810 mg, 8.0 mmol), and concentrated *in vacuo* to a clear, golden yellow oil, which was purified by column chromatography (gradient 20% to 30% to 40% EtOAc in hexanes) to provide diol **10** as a heavy yellow oil (10.1 g, 23 mmol, 86% over 2 steps):

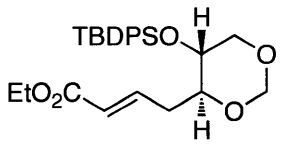
$[\alpha]^{22}_D$ = +21.6 (*c* = 4.9, $CDCl_3$).

IR (thin film, NaCl) 3448, 3072, 2932, 2858, 1718, 1654, 1473, 1428, 1271, 1166, 1112, 1045 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.71-7.66 (m, 4H), 7.49-7.44 (m, 2H), 7.44-7.38 (m, 4H), 6.88 (app dt, *J* = 15.6, 7.3 Hz, 1H), 5.82 (app dt, *J* = 15.7, 1.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.85 (app dq, *J* = 8.8, 4.4 Hz, 1H), 3.73 (ddd, *J* = 11.1, 6.4, 3.7 Hz, 1H), 3.68-3.59 (m, 2H), 2.58 (d, *J* = 4.5 Hz, 1H), 2.44 (dddd, *J* = 14.8, 7.1, 3.8, 1.5 Hz, 1H), 2.28 (dddd, *J* = 14.8, 8.9, 7.4, 1.4 Hz, 1H), 2.08 (app t, *J* = 6.0 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.10 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 145.2, 136.0, 135.9, 133.6, 133.0, 130.4, 130.3, 128.1, 128.1, 124.0, 75.7, 73.0, 63.9, 60.5, 36.1, 27.2, 19.6, 14.5.

HR-MS (ESI) *m/z* calcd for $C_{25}H_{34}O_5Si$ $[M+Na]^+$: 465.2068, found 465.2049.



S1

Methylene acetal S1: To a solution of diol **10** (3.24 g, 7.32 mmol) in CH_2Cl_2 (29 mL) was added first dimethoxymethane (1.04 mL, 890 mg, 11.7 mmol) and then BF_3•OEt_2 (1.48 mL, 1.66 g, 11.7 mmol). The solution, which turned yellow upon addition of BF_3•OEt_2, was stirred 1.25 h. at rt, then quenched with sat. $NaHCO_{3(aq)}$ (~14 mL). The aqueous layer was separated, diluted with brine (~20 mL), and extracted with EtOAc (3x~75 mL). The combined organics were washed with brine (~30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude **S1** as a colorless oil, which was purified by column chromatography (20% EtOAc in hexanes) to afford methylene acetal **S1** as a colorless oil (2.59 g, 5.70 mmol, 78%). R_f of **S1** = 0.55, 20% EtOAc in hexanes. Crude **S1**, which is ~85-90% pure, can also be carried directly into ozonolysis without chromatographic purification to afford aldehyde **S1**, but yield may be slightly lower.

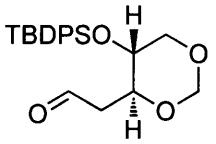
$[\alpha]^{22}_D$ = +14.2 (*c* = 2.6, $CDCl_3$).

IR (thin film, NaCl) 3072, 2932, 2858, 1720, 1657, 1473, 1428, 1267, 1184, 1111, 1033 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.68-7.61 (m, 4H), 7.49-7.44 (m, 2H), 7.44-7.38 (m, 4H), 6.91 (ddd, *J* = 15.7, 7.5, 6.7 Hz, 1H), 5.81 (app dt, *J* = 15.7, 1.5 Hz, 1H), 4.89 (d, *J* = 6.1 Hz, 1H), 4.53 (d, *J* = 6.1 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.90-3.85 (m, 1H), 3.57-3.49 (m, 2H), 3.35 (dd, *J* = 10.7, 9.5 Hz, 1H), 2.73 (app ddt, *J* = 15.1, 6.7, 1.9 Hz, 1H), 2.18 (dddd, *J* = 15.3, 8.6, 7.6, 1.4 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 144.8, 136.0, 135.9, 133.5, 132.9, 130.4, 130.3, 128.1, 128.0, 123.9, 93.4, 81.0, 71.6, 67.3, 60.4, 34.5, 27.1, 19.4, 14.5.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{34}O_5Si$ $[M+Na]^+$: 477.2068, found 477.2080.



11

Aldehyde 11:
Preparation via ozonolysis:

Enoate **S1** (1.00 g, 2.20 mmol) was dissolved in CH_2Cl_2 (22 mL), and the resulting solution cooled to -78 °C. A stream of ozone was bubbled through until a pale blue color evolved, about 2.5 h. Conversion of **S1** may also be monitored by TLC (R_f of **S1** = 0.55; R_f of ozonide = 0.50 (20% EtOAc in hexanes)). Argon was bubbled through the solution to remove residual ozone, and then PPh_3 (664 mg, 2.53 mmol) was added, at which point the cold bath was removed and the reaction was allowed to warm to rt over 1.5 h. The solution was then concentrated *in vacuo* and chromatographed (gradient 5% to 10% to 20% EtOAc in hexanes) to provide aldehyde **11** as a colorless oil (788 mg, 2.05 mmol, 93%): R_f = 0.44 (20% EtOAc in hexanes).

Please note: On large scale (>5 g), ozonolysis was difficult. The reaction times required for full conversion of enoate **S1** stretched to many hours, making the procedure impractical. Furthermore, yields from ozonolysis were lower on large scale. We thus recommend the use of a two step dihydroxylation/oxidative cleavage protocol on large scale.

Preparation via dihydroxylation and oxidative diol cleavage:
To a solution of enoate **S1** (730 mg, 1.6 mmol) in 1:1 v/v H_2O:*t*BuOH (1.6 mL) was added citric acid (252 mg, 1.2 mmol), a solution of NMO in H_2O (50% by weight, 412 mg of solution, 365 μL, 206 mg NMO, 1.76 mmol), and $K_2OsO_2(OH)_4$ (2.9 mg, 0.008 mmol). The resulting grassy green-colored slurry was stirred vigorously for 21 h. at ambient temperature. Over this time the reaction solution became colorless but remained opaque. The reaction was quenched with 1 M $HCl_{(aq)}$ (~ 2 mL), and the crude solution was extracted with Et_2O (3 x ~10 mL), and the combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude diol (R_f = 0.10 (20% EtOAc in hexanes)), which was carried into oxidative cleavage without further purification.

The crude diol from the preceding step was dissolved in 1:1 v/v THF:H_2O (8.0 mL). The solution was cooled to 0 °C, and $NaIO_4$ (1.03 g, 4.8 mmol) was added. The reaction mixture was stirred vigorously for 1.5 h. at 0 °C. It was then quenched by dilution with H_2O (~15 mL). The mixture was extracted with EtOAc (3 x ~30 mL), and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purifed by column chromatography (gradient 5% to 40% EtOAc in hexanes) to provide aldehyde **11** (505 mg, 1.31 mmol, 82% over 2 steps, R_f = 0.49 (20% EtOAc in hexanes)).

$[\alpha]^{22}_D$ = -6.5 (*c* = 1.26, CH_2Cl_2).

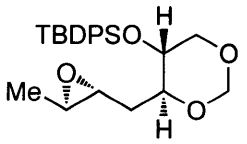
IR (thin film, NaCl) 3072, 2932, 2858, 1729, 1473, 1428, 1217, 1171, 1111, 1066, 1035 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (dd, *J* = 2.6, 1.4 Hz,1H), 7.68-7.61 (m, 4H), 7.51-7.38 (m, 6H), 4.87 (d, *J* = 6.2 Hz, 1H), 4.58 (d, *J* = 6.2 Hz, 1H), 4.00 (app td, *J* = 9.0, 2.8 Hz, 1H), 3.90 (dd, *J* = 10.7, 4.9 Hz, 1H), 3.57 (app td, *J* = 9.4, 5.0 Hz, 1H), 3.40 (app t, *J* = 10.3 Hz, 1H), 2.80 (ddd, *J* = 16.6, 2.8, 1.4 Hz, 1H), 2.41 (ddd, *J* = 16.6, 9.1, 2.7 Hz,

1H), 1.06 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 135.9, 135.9, 133.3, 132.7, 130.5, 130.4, 128.2, 128.0, 93.3, 77.5, 71.6, 67.1, 45.8, 27.1, 19.4.

HR-MS (ESI) *m/z* calcd for $C_{22}H_{28}O_4Si$ $[M+Na]^+$: 407.1649, found 406.1660.



13

Epoxide 13: A dry round bottom flask was charged with $CrCl_2$ (1.92 g, 15.6 mmol), to which was added dry THF (20 mL) to afford a pale green slurry. Meanwhile, aldehyde **11** (500 mg, 1.30 mmol) was added to a dry round bottom flask, and the flask was evacuated on high vac and backfilled with argon. This procedure was repeated, and then **11** was dissolved in dry THF (3 mL). 1,1-diiodoethane[17] (1.1 g, 3.9 mmol) was added, and this mixture of was added dropwise to the $CrCl_2$ slurry. The flask contained **11** and $MeCHI_2$ was washed out with a further portion of dry THF (3 mL), which was added to the reaction flask. The mixture was stirred at rt for 3.5 h., over which time the color changed from pale green to chocolate brown. The reaction was then quenched by pouring into brine (~50 mL). The aqueous layer was separated and extracted with Et_2O (4x~100 mL), and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude alkene as an orange-brown oil. ^{1}H NMR analysis revealed this material to be of ~91:9 *E*:*Z* stereopurity, and to contaminated with some unreacted 1,1-diiodoethane, which does not adversely affect the next step. This crude material was carried forward into Shi epoxidation without further purification (R_f of alkene = 0.64 (10% EtOAc in hexanes)).

To a solution of this crude alkene in 2:1 v/v DMM:MeCN (48 mL) was added a 0.05 M solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} Na_2EDTA (24 mL), $n$$Bu_4HSO_4$ (98 mg, 0.066 mmol), and chiral ketone **12** (455 mg, 1.76 mmol). This biphasic mixture was stirred vigorously at 0 °C. To this mixture was added, simultaneously over 40 min. via syringe pump, a solution of Oxone (4.32 g, 7.02 mmol) in 4 x 10^{-4} Na_2EDTA (15.8 mL) and a 0.89 M solution of K_2CO_3 (15.8 mL, 14.0 mmol). After the K_2CO_3 and Oxone solutions had been added, the resulting mixture was stirred an additional 60 min., at which point it was diluted with water (~100 mL). The aqueous layer was separated and extracted with EtOAc (3x100 mL), and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. ^{1}H NMR analysis at this point indicated incomplete conversion, so the crude material was subjected again to identical epoxidation

[17] 1,1-Diiodoethane was prepared according the procedure of Letsinger and Kammeyer; see: Letsinger, R. L.; Kammeyer, C. W. *J. Am. Chem. Soc.*, **1951**, *73*, 3376.

conditions and worked up as before. The crude epoxide **13** was chromatographed (gradient 3% to 25% EtOAc in hexanes) to provide **13**, a colorless oil, as an inseparable mixture of diastereomers (408 mg of a <10:1 mixture of diastereomers, 0.99 mmol combined, 76% over 2 steps), R_f = 0.56 (20% EtOAc in hexanes). Epoxide **13** could be purified slightly further via preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 0.4% *i*PrOH in hexanes, 20 mL/min.; t_R of major and minor diastereomers = 7.3 min.; collect only the first ¼ of the peak to obtain material in high dr) to afford **13** in 10:1-15:1 dr. Better purification was achieved by running **13** through a Biotage high performance silica gel column (Biotage® SNAP HP-Sil, gradient 7% to 40% EtOAc in hexanes)). The two diastereomers cospot by TLC, but early fractions are enriched in the minor diastereomer and late fractions are high purity **13** (30:1 dr by ^{1}H NMR).

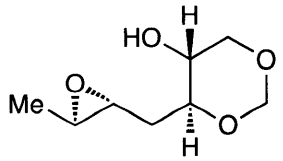
$[\alpha]^{22}_D$ = -6.6 (*c* = 0.81, $CDCl_3$).

IR (thin film, NaCl) 3072, 2931, 2857, 1473, 1428, 1176, 1112, 1037 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.61 (m, 4H), 7.48-7.43 (m, 2H), 7.43-7.37 (m, 4H), 4.90 (d, *J* = 6.1 Hz, 1H), 4.55 (d, *J* = 6.1 Hz, 1H), 3.84 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.58-3.51 (m, 2H), 3.37-3.30 (m, 1H), 2.77-2.70 (m, 2H), 1.96 (ddd, *J* = 14.5, 5.8, 1.8 Hz, 1H), 1.72 (ddd, *J* = 13.8, 8.3, 5.0 Hz, 1H), 1.28 (d, *J* = 5.1 Hz, 3H), 1.04 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 135.9, 133.7, 132.9, 130.3, 130.2, 128.1, 127.9, 93.3, 80.3, 71.6, 67.4, 56.8, 54.2, 34.1, 27.1, 19.5, 17.8.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{32}O_4Si$ $[M+Na]^+$: 435.1962, found 435.1975.



4

Epoxy alcohol 4: To a solution of silyl ether **13** (102 mg, 0.248 mmol) in THF (400 μL) was added a 1M solution of TBAF in THF (497 μL, 0.497 mmol). The reaction solution was stirred at rt for 20 min., then applied directly to a column of SiO_2 (eluted with a gradient 30% to 100% EtOAc in hexanes) to yield **4** as a colorless oil (38.4 mg, 0.220 mmol, 89%).

$[\alpha]^{22}_D$ = +2.1 (*c* = 1.00, CH_2Cl_2).

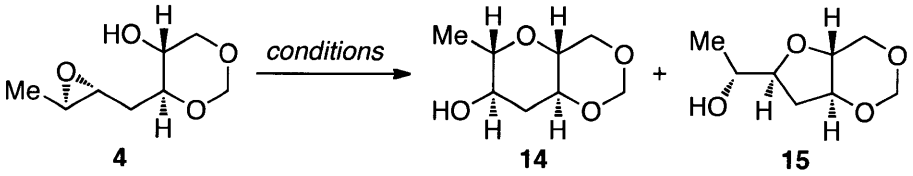
IR (thin film, NaCl) 3423, 2964, 2923, 2853, 2774, 1653, 1457, 1438, 1381, 1257, 1225,

1175, 1150, 1073, 1028 cm^{-1}.

^1H NMR (500 MHz, C_6D_6) δ 4.90 (d, J = 6.0 Hz, 1H), 4.25 (d, J = 6.0 Hz, 1H), 4.05 (dd, J = 10.6, 5.1 Hz, 1H), 3.61 (app td, J = 9.5, 5.2 Hz, 1H), 3.24 (ddd, J = 9.3, 5.6, 4.0 Hz, 1H), 3.15 (app t, J = 10.3 Hz, 1H), 2.82 (ddd, J = 6.5, 3.8, 2.3 Hz, 1H), 2.48 (qd, J = 5.2, 2.2 Hz, 1H), 2.43 (br s, 1H), 1.93 (app dt, J = 14.9, 3.9 Hz, 1H), 1.71 (ddd, J = 14.9, 6.7, 5.8 Hz, 1H), 0.98 (d, J = 5.2 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 93.6, 80.2, 71.6, 65.9, 56.5, 54.3, 34.8, 17.8.

HR-MS (DART) *m/z* calcd for $C_8H_{14}O_4$ $(M+H)^+$: 175.0965, found 175.0973.



4 **14** **15**

Procedures for Cyclization Reactions of 4.

Representative procedure for reaction in **water or buffered water**:
A sample of diepoxy alcohol **4** (1-2 mg, 5.7-11 μmol, 30:1 dr) was dissolved in deionized water to 0.02 M in a glass vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was stirred at ambient temperature for 60 days. The solution was then washed out of the reaction vial with a large volume of MeOH (typically 6-8 washes of ~1 mL each) and concentrated *in vacuo* (2 torr, 40°). The crude ratio **14**:**15** was determined by ^1H NMR. The crude product mixture was chromatographed (30% EtOAc in hexanes to 50% EtOAc in hexanes) to separate the *endo* product, 6,6-fused **14** (R_f = 0.65 (100% EtOAc)) from the *exo* product, 6,5-fused **15** (R_f = 0.53 (100% EtOAc)).

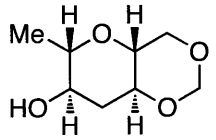
Representative procedure for reaction promoted by **Cs_2CO_3**:
A sample of diepoxy alcohol **4** (1-2 mg, 5.7-11 μmol, 30:1 dr) was dissolved in a solution of Cs_2CO_3 (30 equiv) in anhydrous MeOH to 0.02 M in a glass vial. The threads of the vial were lined with Teflon tape, the cap was sealed and covered with parafilm, and the solution was stirred under air at rt for 1-2 days. The solution was then diluted with Et_2O, quenched with sat. NH_4Cl, and the aqueous layer was extracted with Et_2O. The combined organics were concentrated *in vacuo* without drying, and the crude ratio **14**:**15** was determined by ^1H NMR. The crude product mixture was chromatographed (30% EtOAc in hexanes to 50% EtOAc in hexanes) to separate the *endo* product, 6,6-fused **14** (R_f = 0.65 (100% EtOAc)) from the *exo* product, 6,5-fused **15** (R_f = 0.53 (100% EtOAc)).

Representative procedure for reaction promoted by **CSA**:
A sample of diepoxy alcohol **4** (1-2 mg, 5.7-11 μmol, 30:1 dr) was dissolved in CH_2Cl_2

to 0.02 M in an oven-dried round-bottom flask. To this was added (+/-)-CSA (1 equiv), and the solution was stirred under argon at rt for 4-15 hours. The solution was then quenched with sat. $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The combined organics were concentrated *in vacuo* without drying, and the crude ratio **14**:**15** was determined by ^1H NMR. The crude product mixture was chromatographed (30% EtOAc in hexanes to 50% EtOAc in hexanes) to separate the *endo* product, 6,6-fused **14** (R_f = 0.65 (100% EtOAc)) from the *exo* product, 6,5-fused **15** (R_f = 0.53 (100% EtOAc)).

Representative procedure for reaction promoted by **BF_3**:
A sample of diepoxy alcohol **4** (1-2 mg, 5.7-11 μmol, 30:1 dr) was dissolved in CH_2Cl_2 to 0.02 M in an oven-dried round-bottom flask and cooled to -78 °C. To this was added, dropwise, a 0.1 M solution of BF_3•OEt_2 in CH_2Cl_2 (0.25 equiv), and the solution was stirred at -78 °C under argon for 30 min. The solution was then allowed to warm gradually to rt over 5 min. and quenched with sat. $NaHCO_3$. The aqueous layer was extracted with Et_2O, and the combined organics were concentrated *in vacuo* without drying, and the crude ratio **14**:**15** was determined by ^1H NMR. The crude product mixture was chromatographed (30% EtOAc in hexanes to 50% EtOAc in hexanes) to separate the *endo* product, 6,6-fused **14** (R_f = 0.65 (100% EtOAc)) from the *exo* product, 6,5-fused **15** (R_f = 0.53 (100% EtOAc)).

Representative procedure for reaction promoted by **SiO_2**:
A sample of diepoxy alcohol **4** (1-2 mg, 5.7-11 μmol, 30:1 dr) was dissolved in CH_2Cl_2 to 0.02 M in an oven-dried round-bottom flask. To this was added flame-dried silica gel (90 mg per mmol **4**), and the suspension was stirred at ambient temperature for 11 days. The cyclization products were stripped from SiO_2 by repeated washing with a solution of 5% MeOH in Et_2O. The solution was filtered and concentrated *in vacuo* without drying, and the crude ratio **14**:**15** was determined by ^1H NMR. The crude product mixture was chromatographed (30% EtOAc in hexanes to 50% EtOAc in hexanes) to separate the *endo* product, 6,6-fused **14** (R_f = 0.65 (100% EtOAc)) from the *exo* product, 6,5-fused **15** (R_f = 0.53 (100% EtOAc)).



14

6,6-Fused bicycle 14: R_f = 0.65 (100% EtOAc).

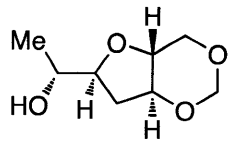
$[\alpha]^{22}_D$ = -8.8 (*c* = 0.15, CH_2Cl_2).

IR (thin film, NaCl) 3365, 2963, 2923, 2862, 1463, 1401, 1349, 1279, 1211, 1161, 1118, 1075, 1059, 1024 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (d, J = 6.2 Hz, 1H), 4.62 (d, J = 6.2 Hz, 1H), 4.18 (dd, J = 10.4, 4.2 Hz, 1H), 3.44-3.36 (m, 2H), 3.34-3.23 (m, 3H), 2.43 (app dt, J = 11.4, 4.3 Hz, 1H), 1.61 (app q, J = 11.2 Hz, 1H), 1.56 (s, 1H), 1.30 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 93.9, 78.8, 76.8, 73.5, 71.6, 69.4, 38.3, 18.0.

HR-MS (DART) *m/z* calcd for $C_8H_{14}O_4$ $(M+H)^+$: 175.0965, found 175.0967.



15

6,5-Fused bicycle 15: R_f = 0.53 (100% EtOAc).

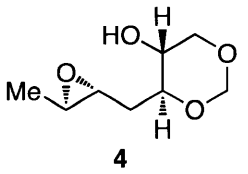
$[\alpha]^{22}_D$ = -17.9 (c = 0.045, CH_2Cl_2).

IR (thin film, NaCl) 3450, 2921, 2851, 1463, 1256, 1155, 1126, 1053 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (d, J = 6.2 Hz, 1H), 4.63 (d, J = 6.2 Hz, 1H), 4.40 (dd, J = 9.7, 3.7 Hz, 1H), 4.07-4.00 (m, 2H), 3.58 (app t, J = 9.6 Hz, 1H), 3.48-3.40 (m, 2H), 2.23 (app dt, J = 11.1, 5.8 Hz, 1H), 2.09 (app dt, J = 11.1, 9.2 Hz, 1H), 1.86 (d, J = 3.8 Hz, 1H), 1.18 (d, J = 6.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 94.2, 81.8, 80.7, 73.8, 72.0, 69.1, 29.3, 18.2.

HR-MS (DART) *m/z* calcd for $C_8H_{14}O_4$ $(M+Na)^+$: 197.0784, found 197.0794.



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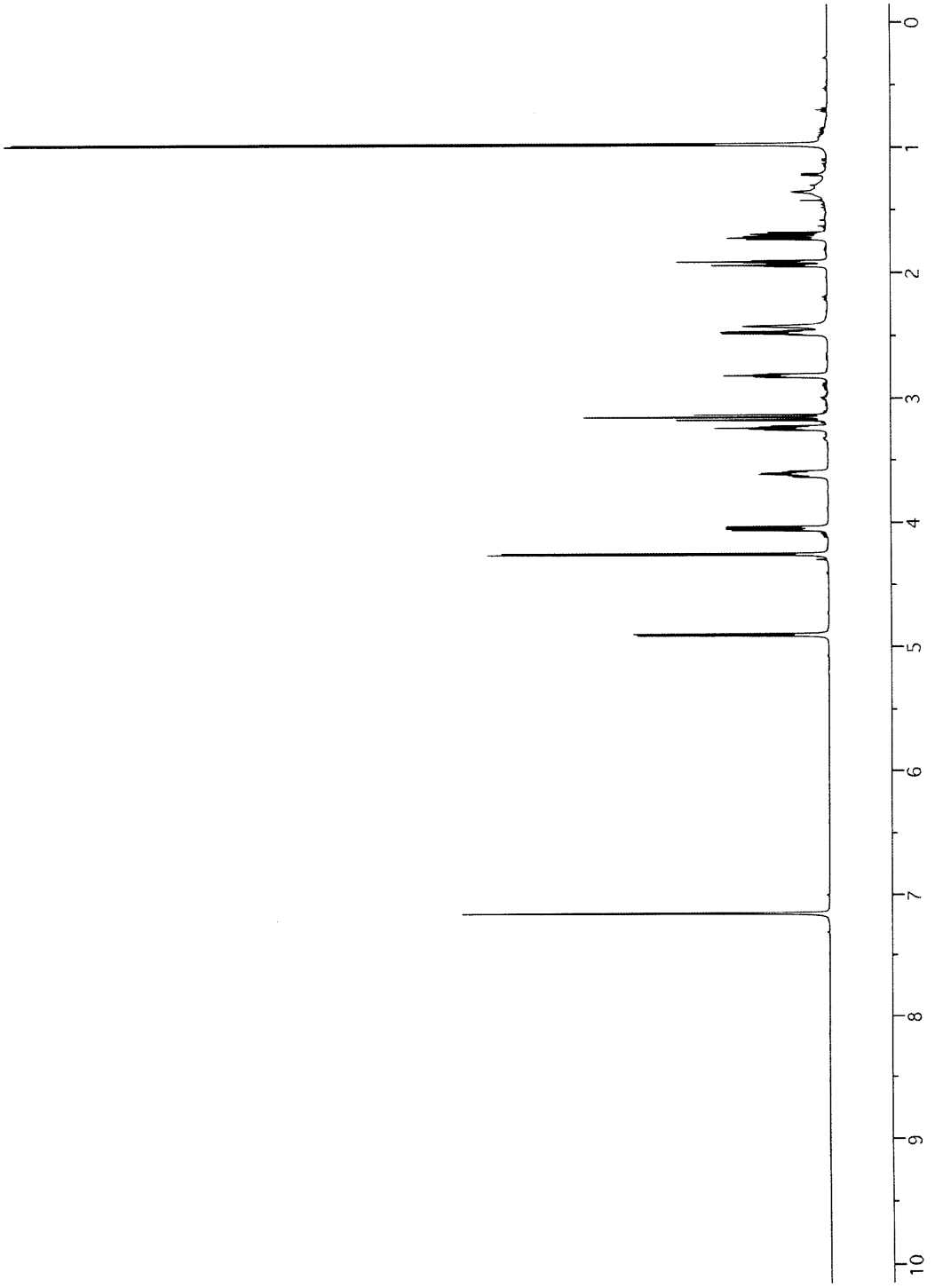

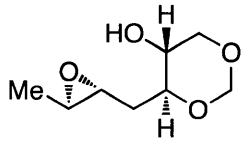

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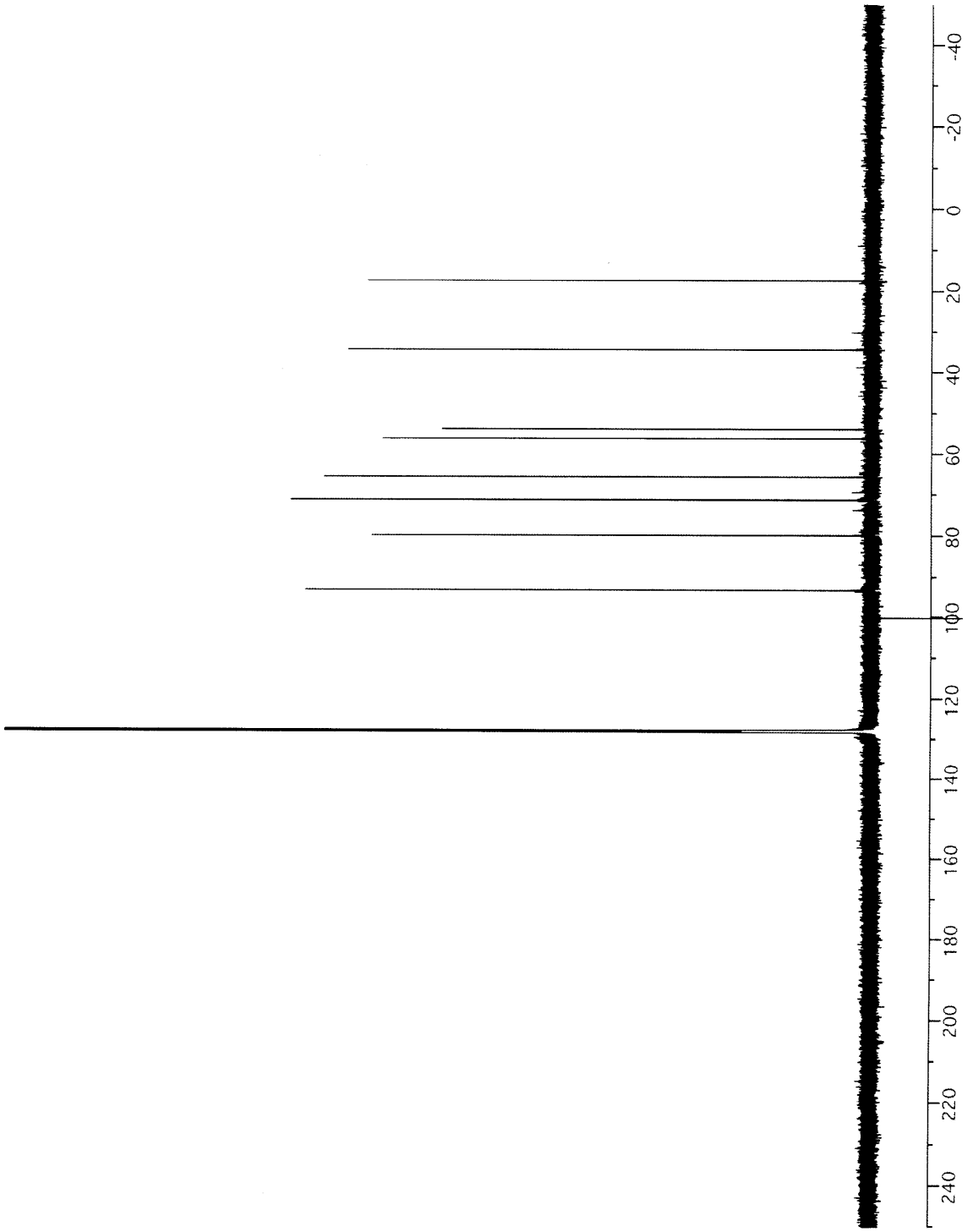

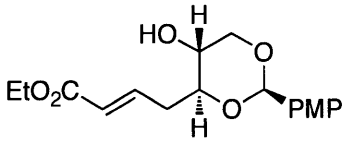

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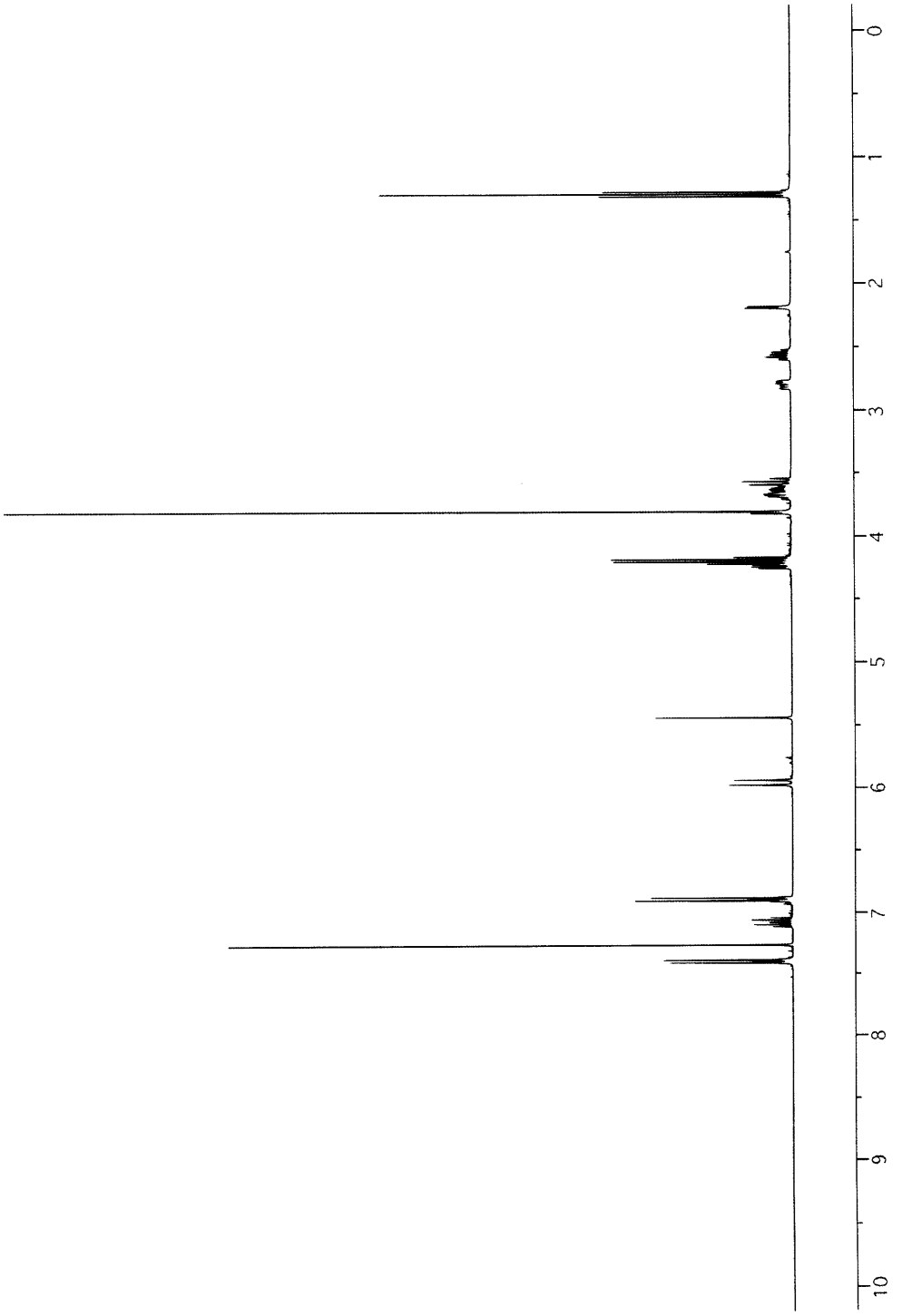

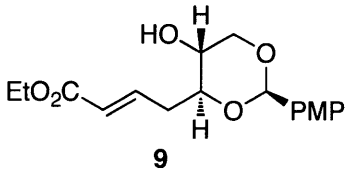

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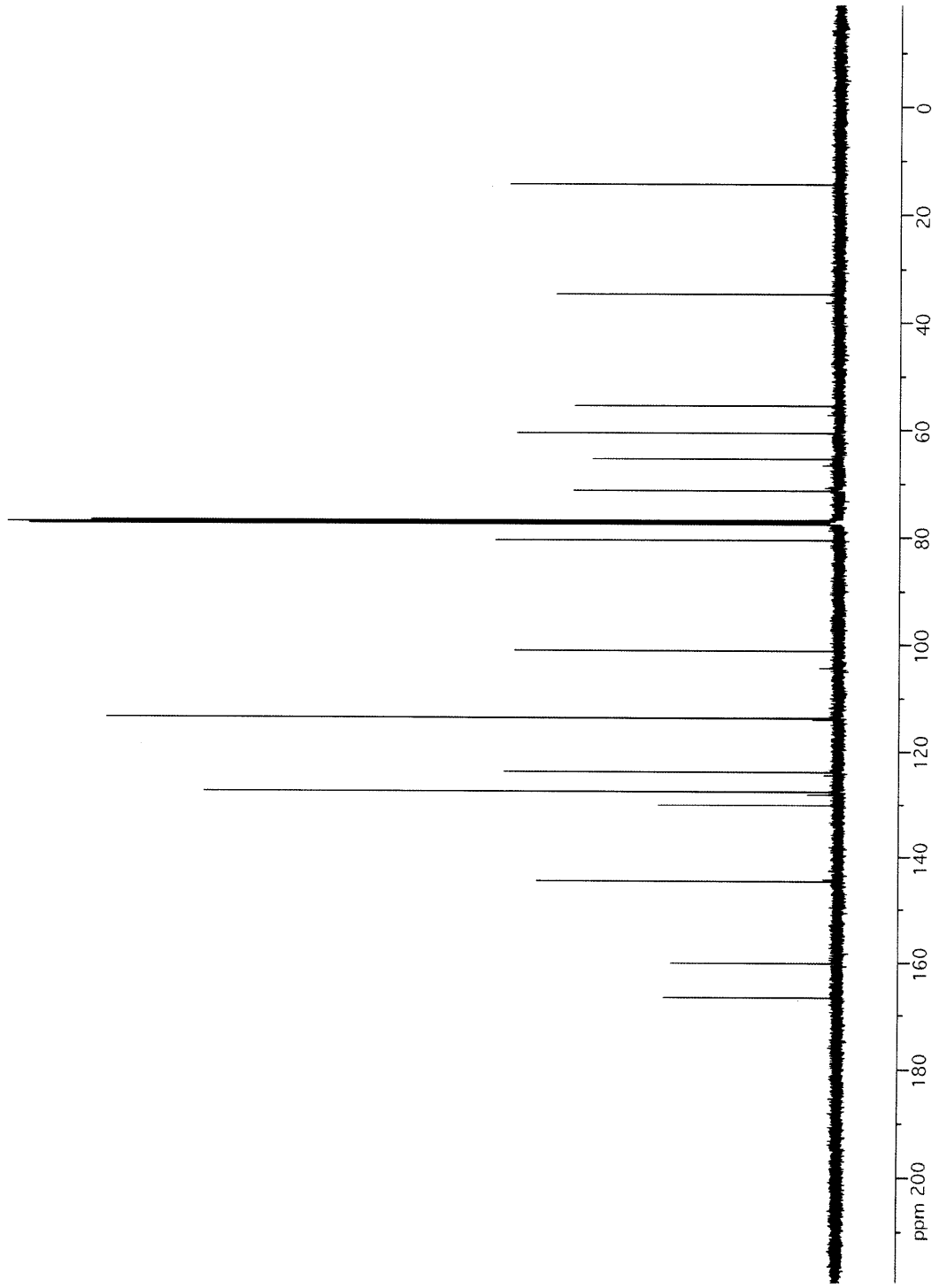

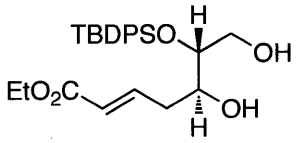

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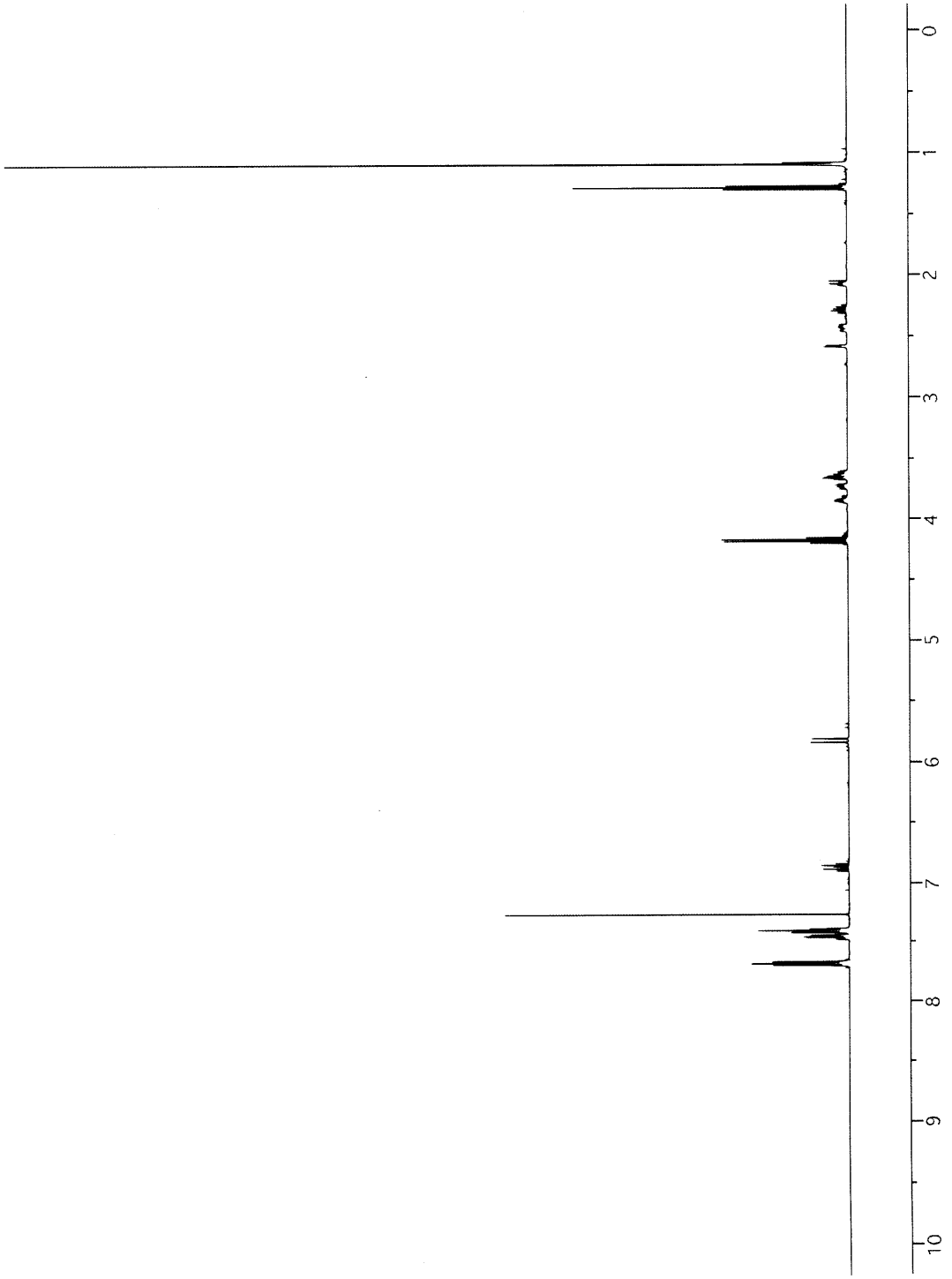

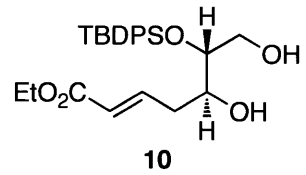

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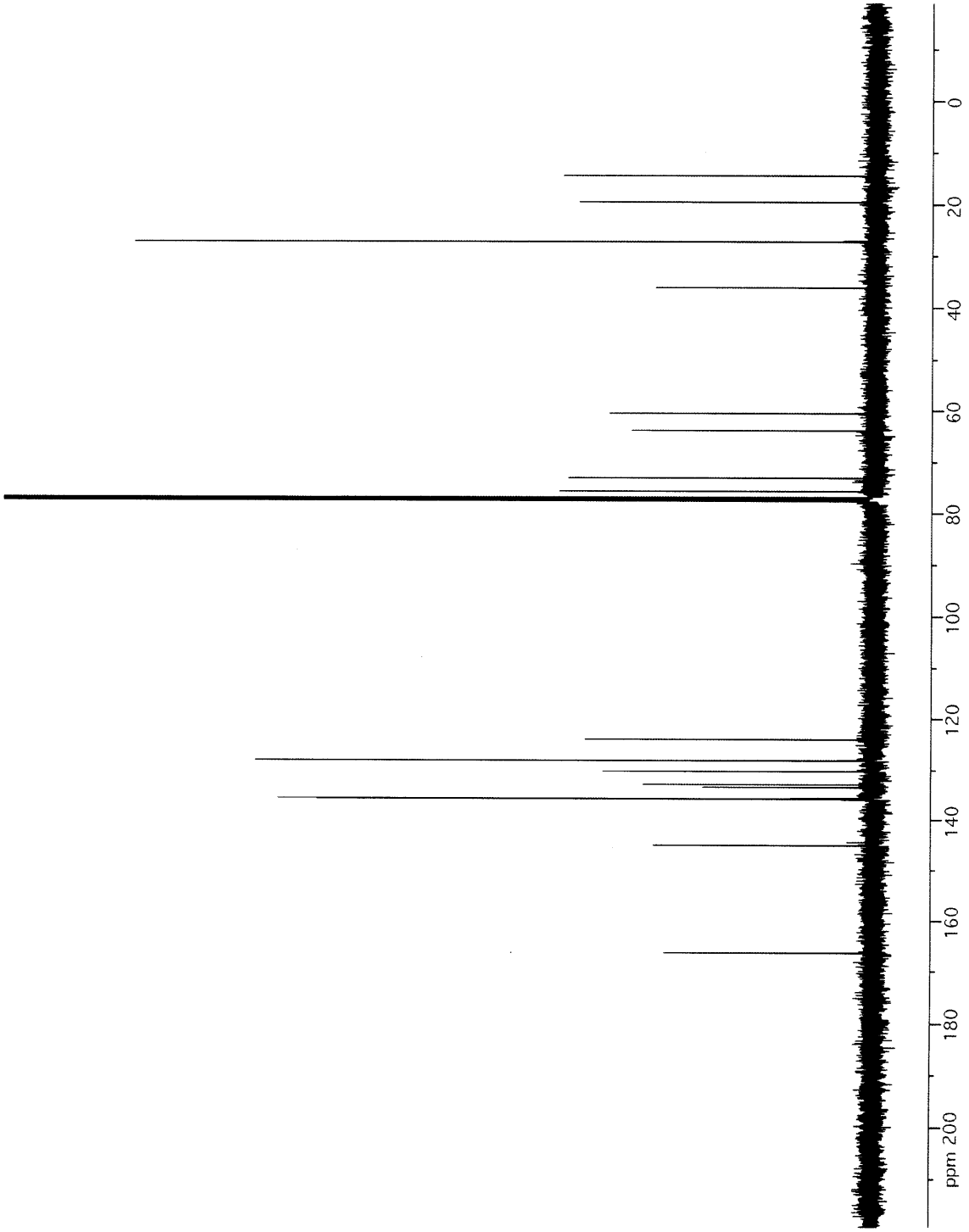

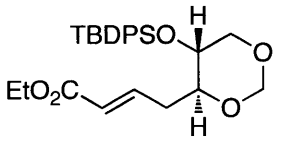

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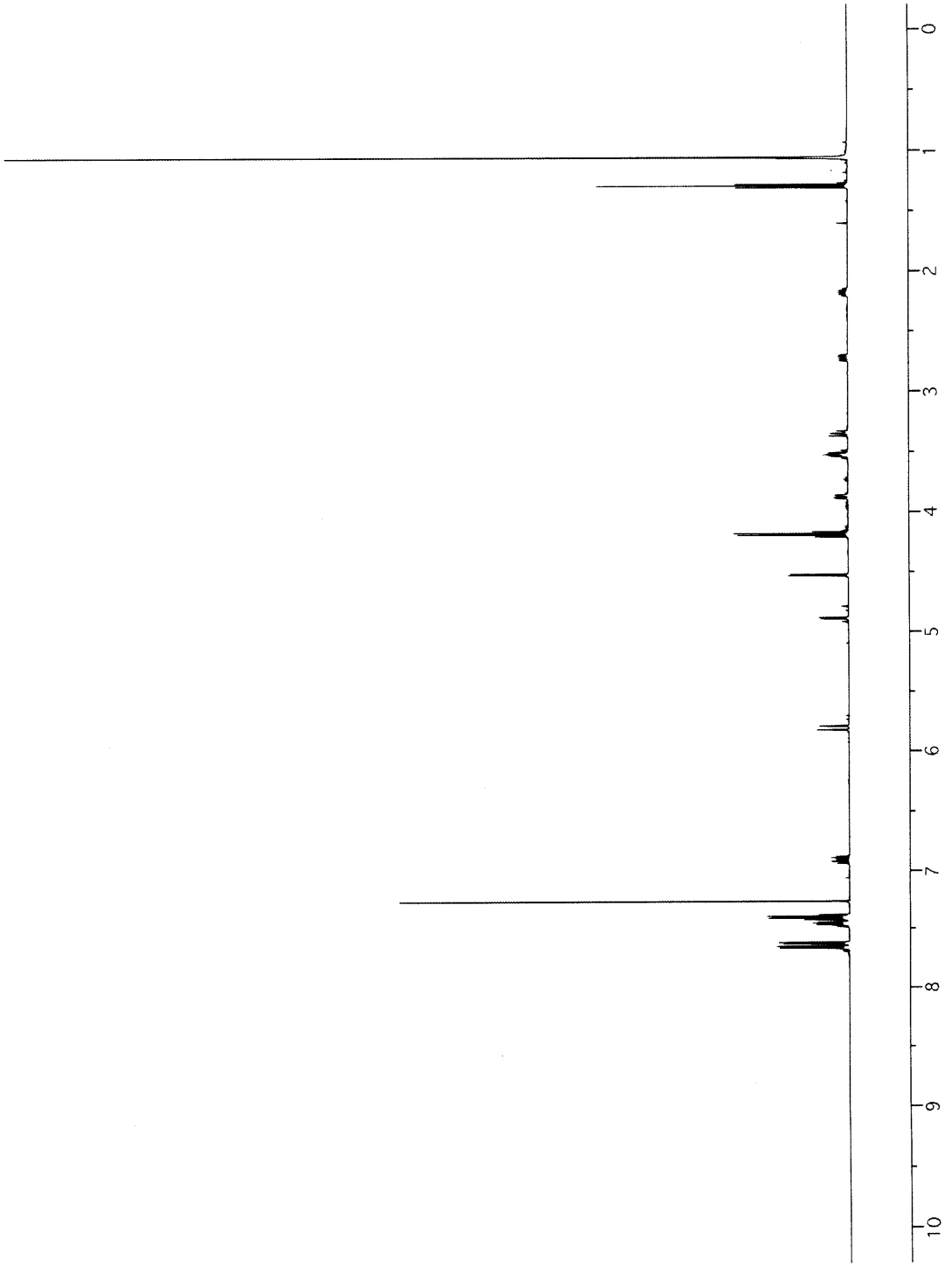

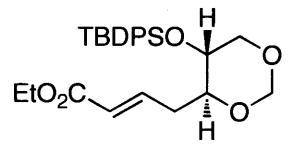

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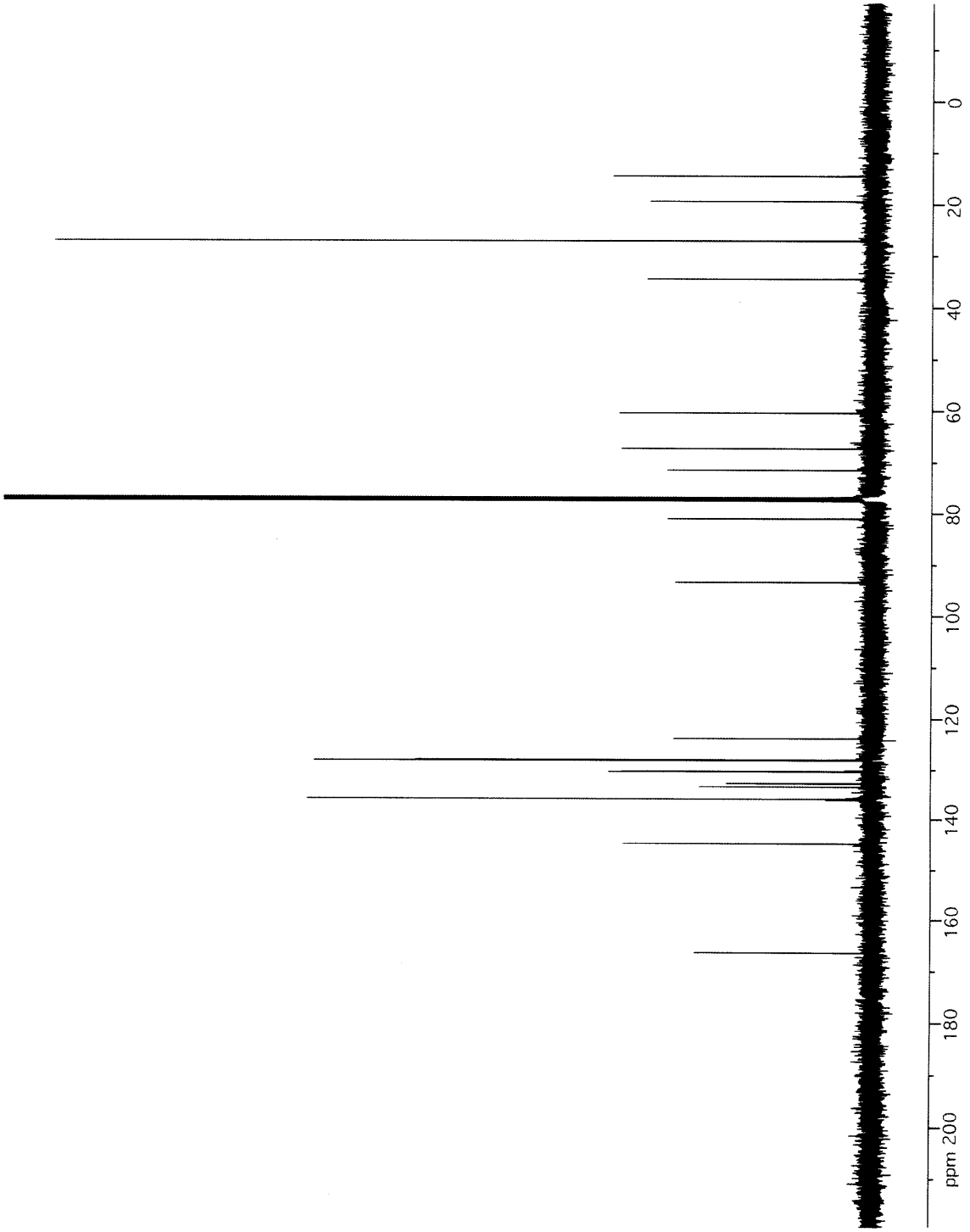

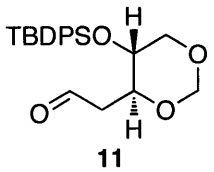

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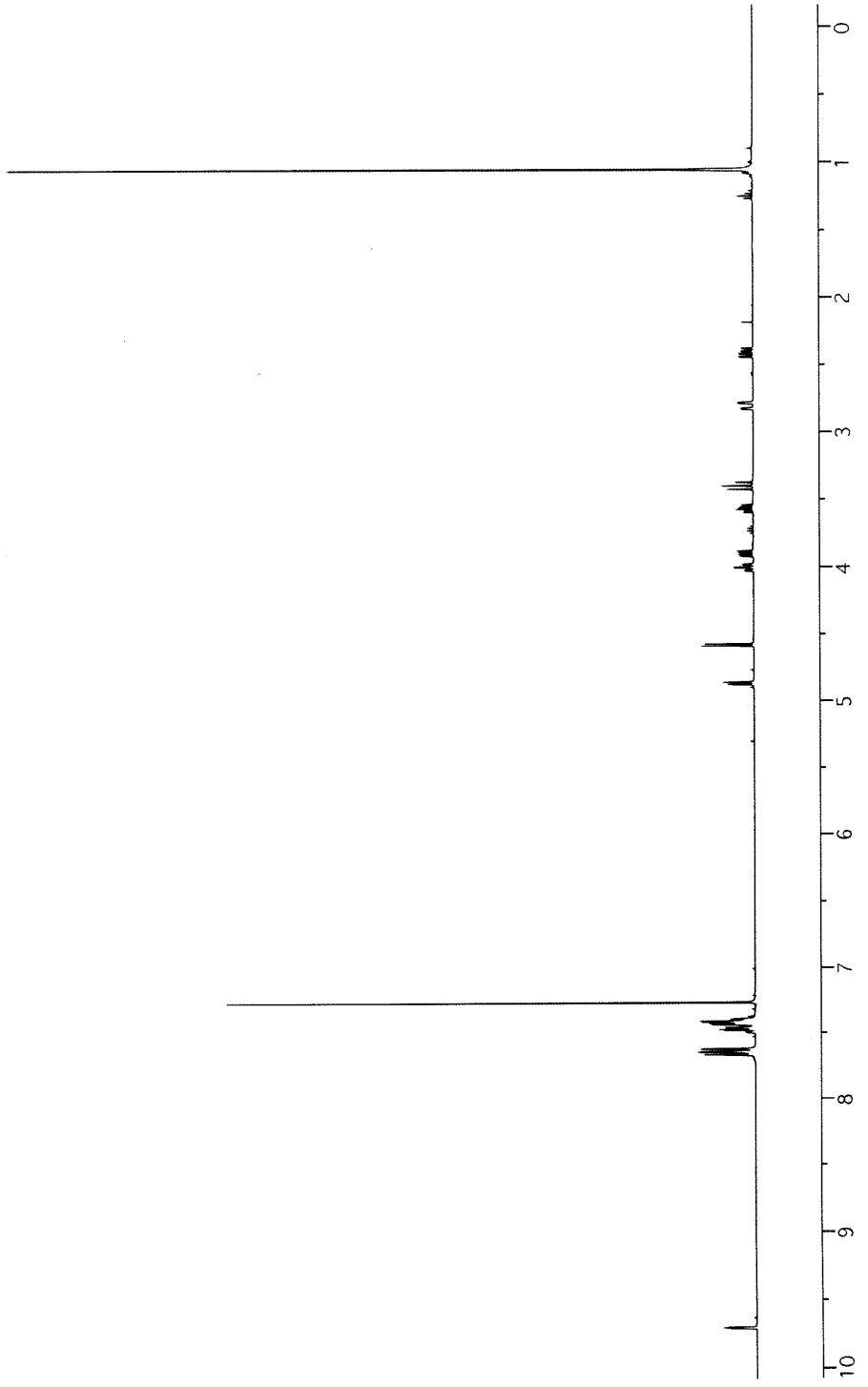

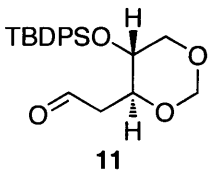

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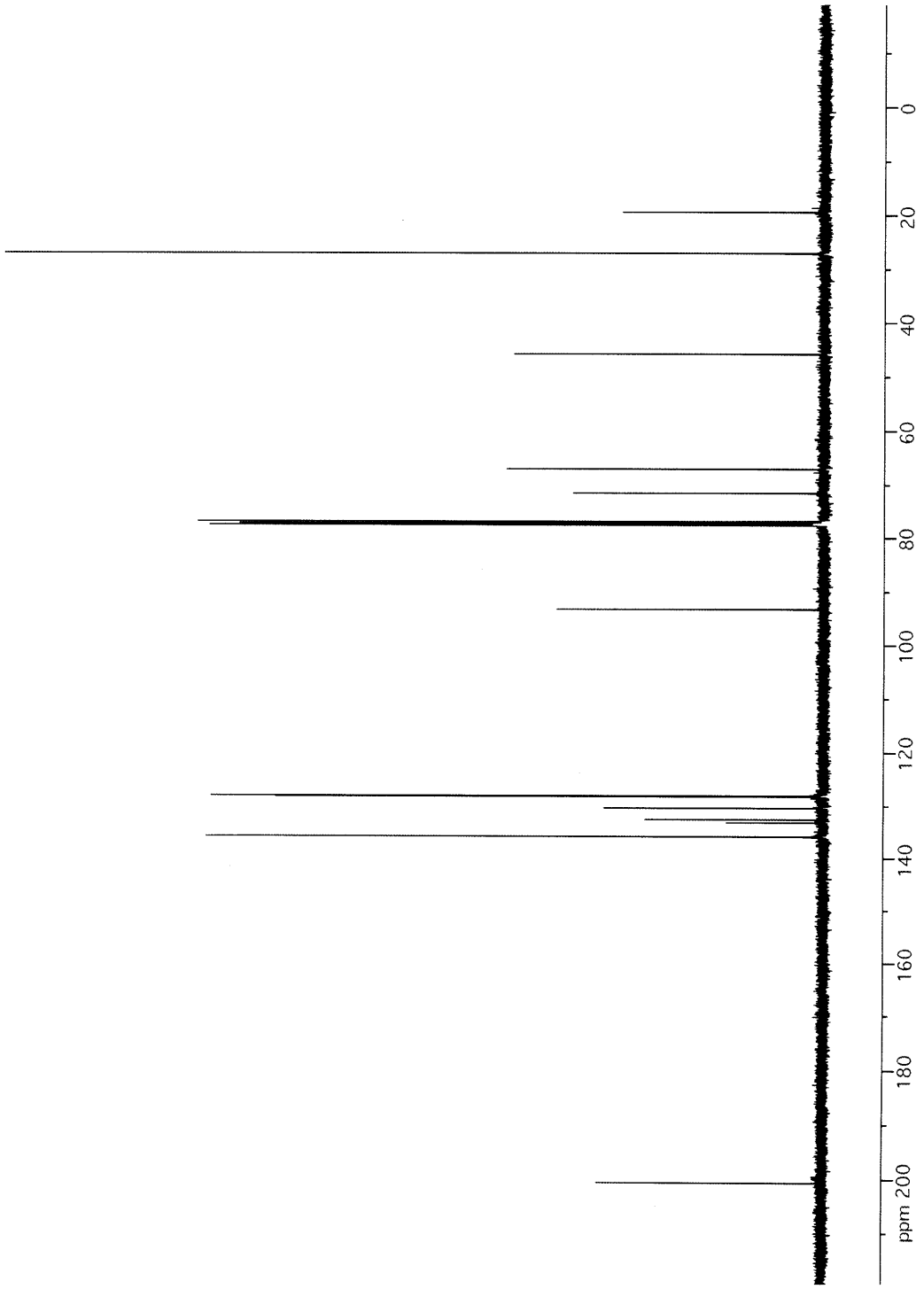

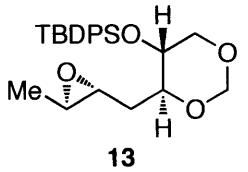

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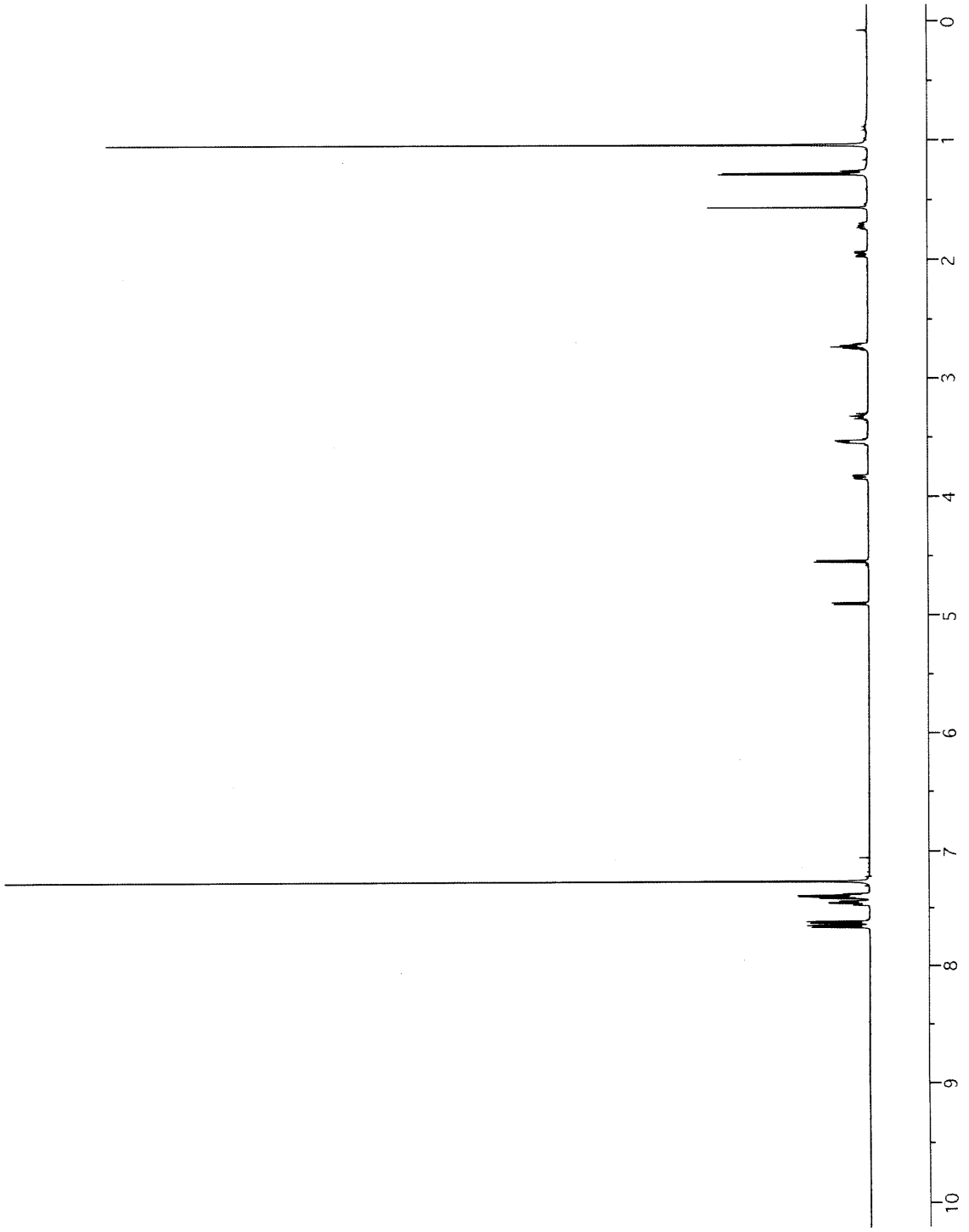

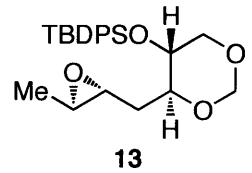

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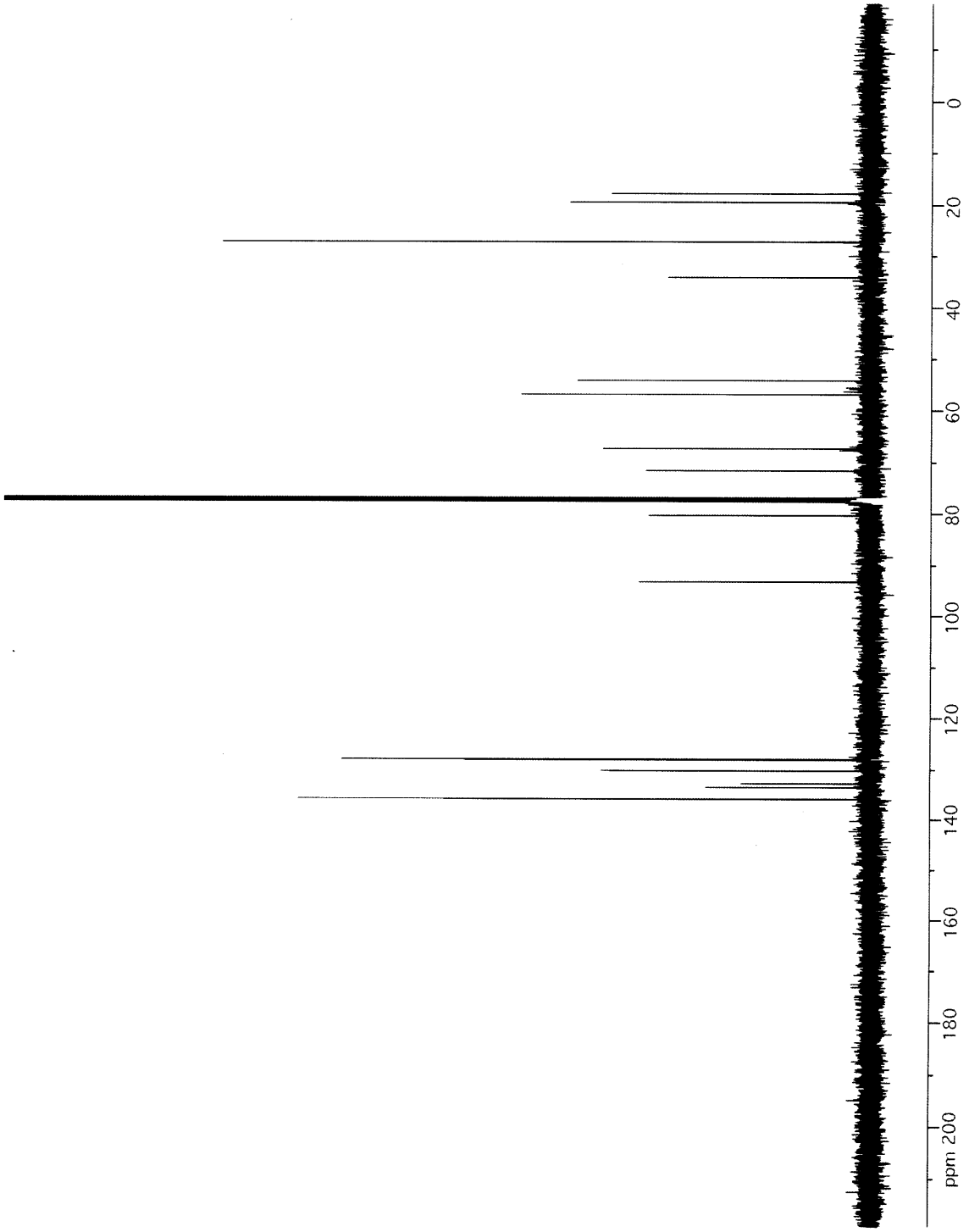

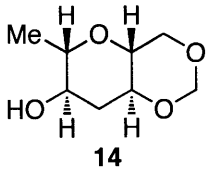

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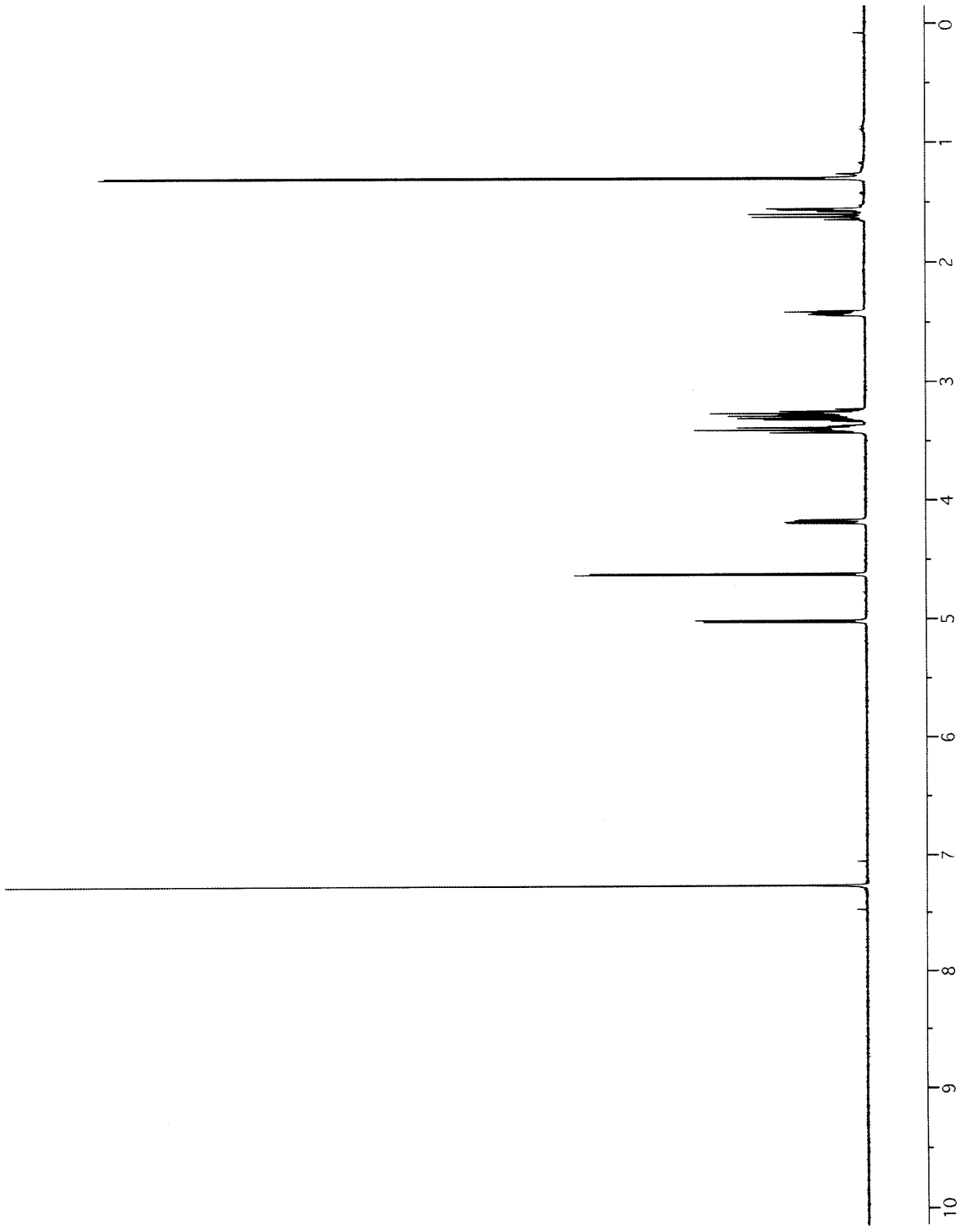

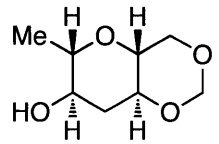

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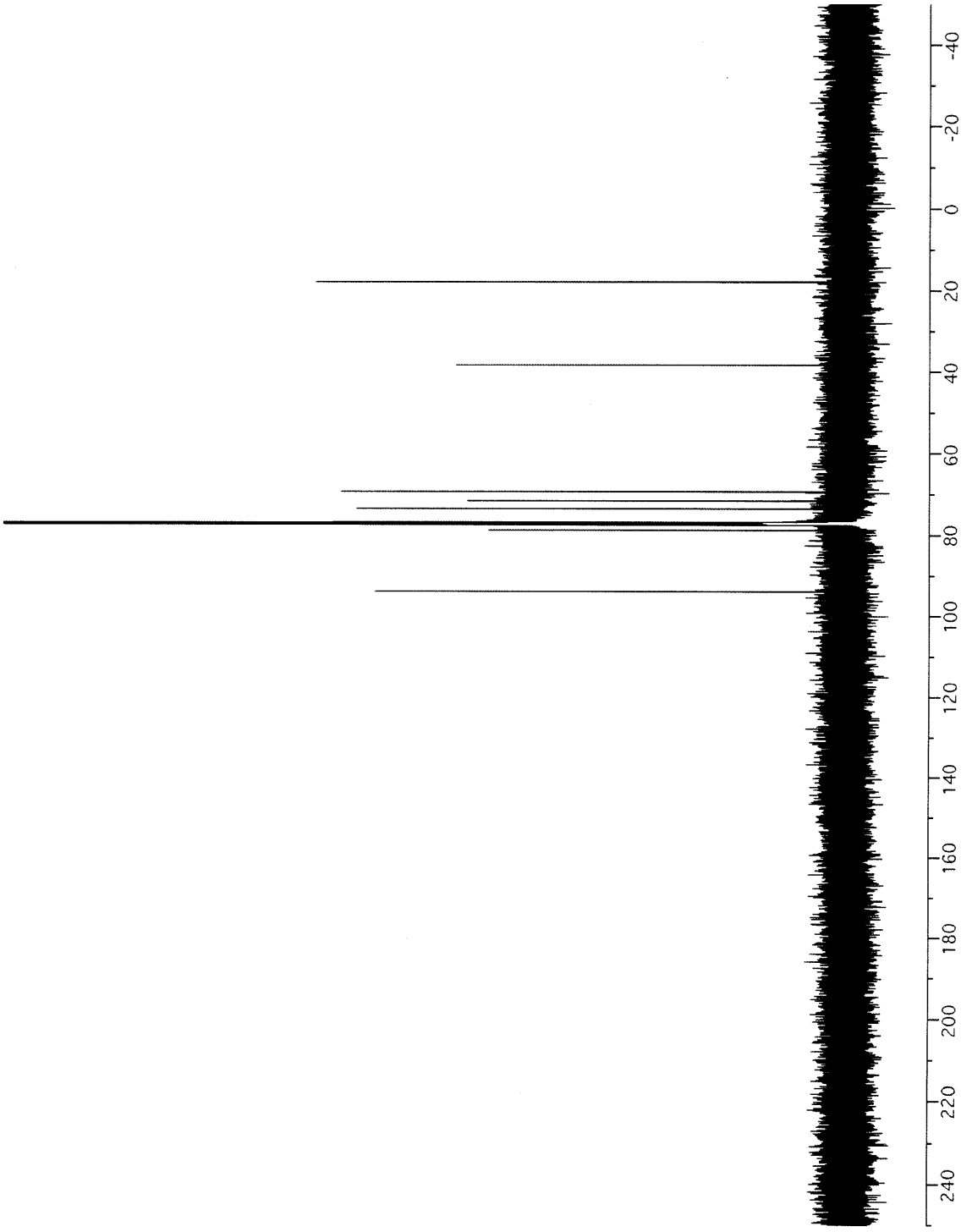

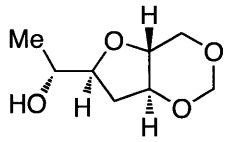

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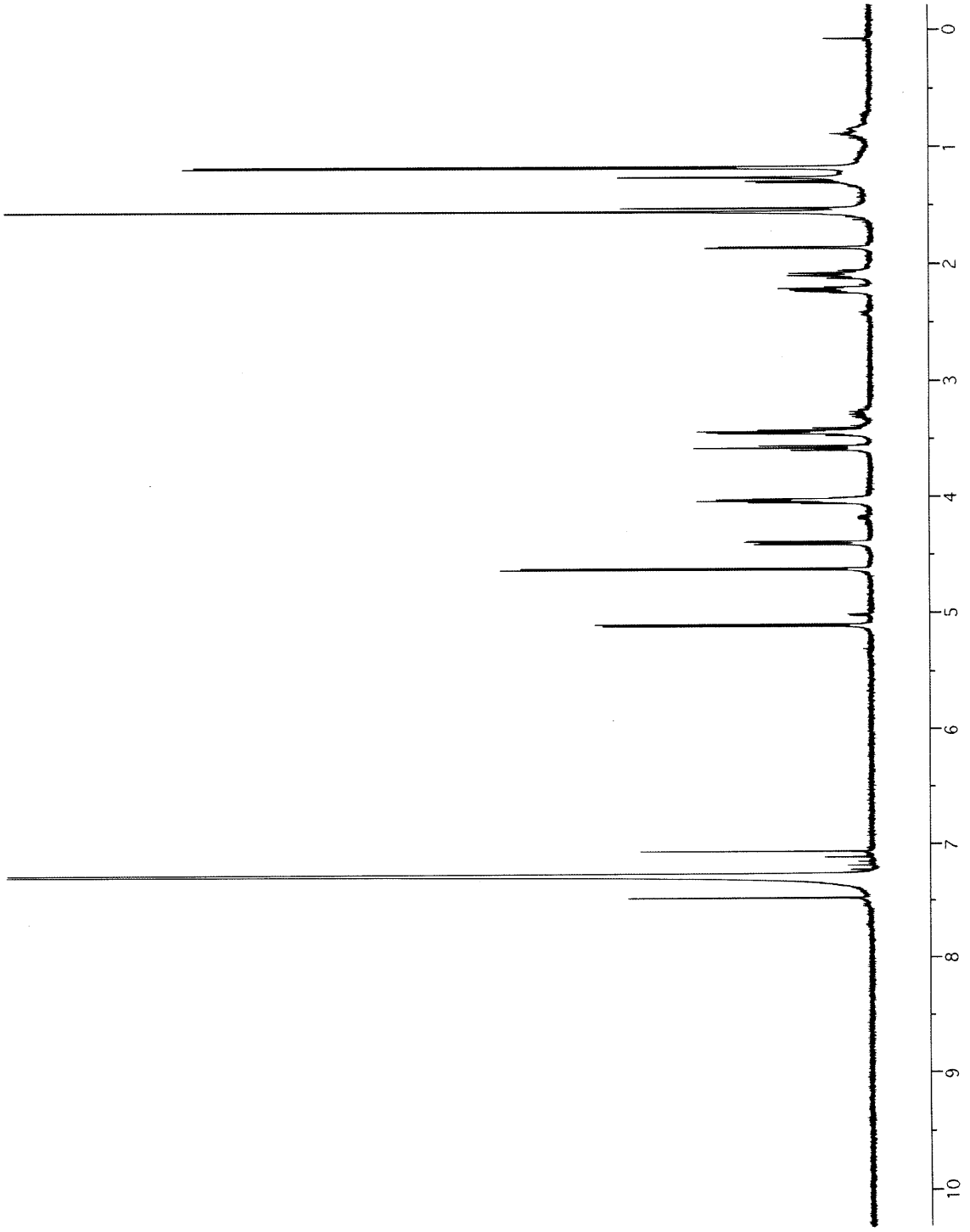

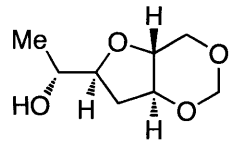

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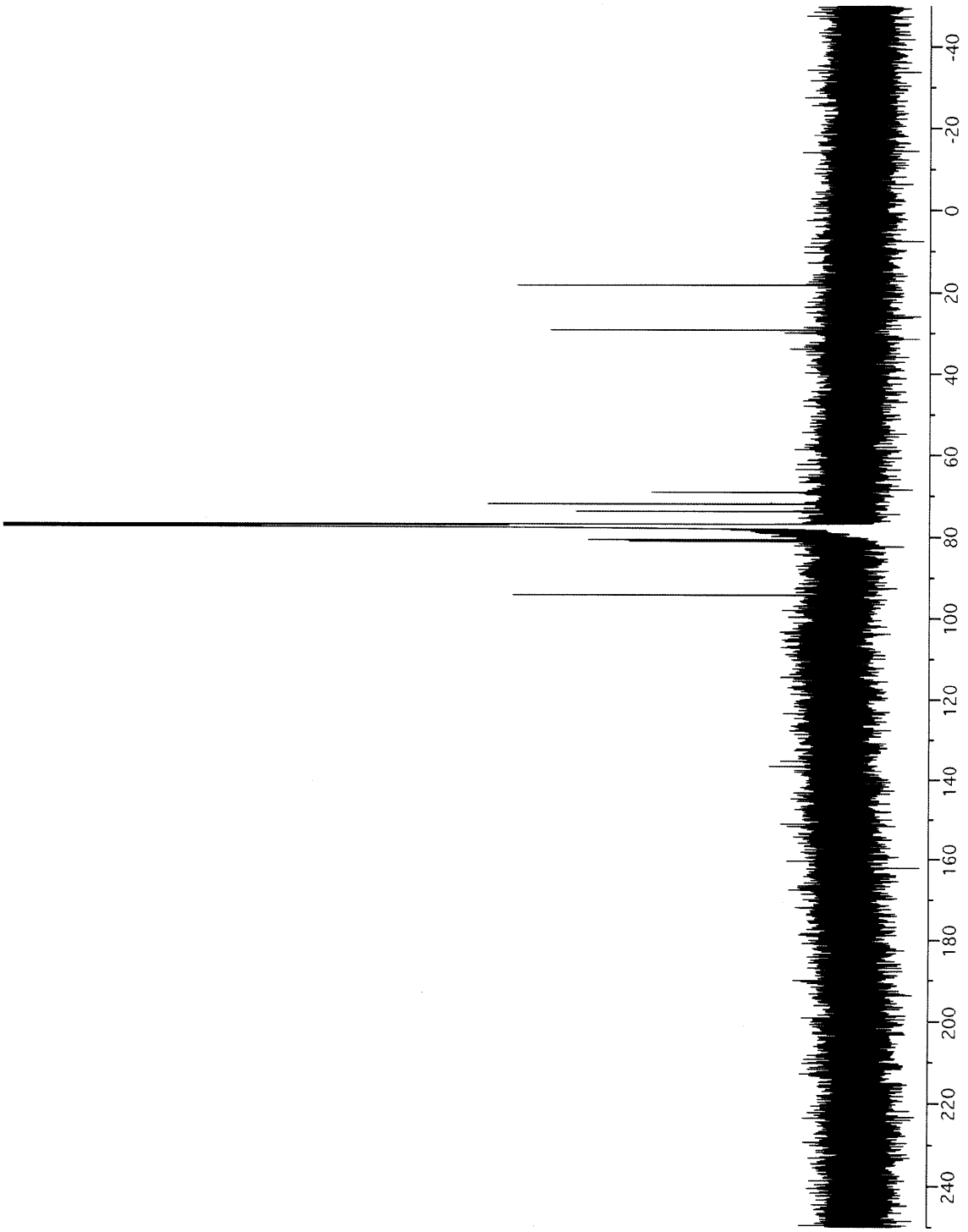


Chapter V

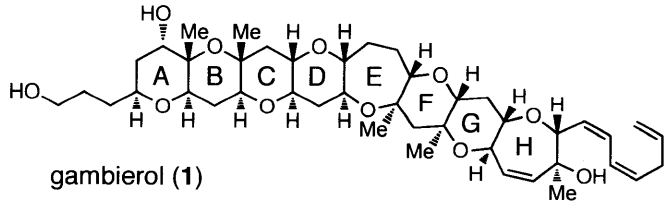
Progress Toward the Synthesis of Gambierol via *Endo*-Selective Epoxide-Opening Cascades Promoted by Water.

A. Introduction to gambierol and its biological activity.

In Chapter III, we elucidated a stepwise mechanism for an *endo*-selective epoxide-opening cascade in water. In Chapter IV, we described a versatile methylene acetal template for *endo* epoxide opening. With a better understanding of cascade mechanism and a potentially useful new template, we began to consider a larger challenge: the biomimetic total synthesis of an entire ladder polyether. At this point we had tested our water-promoted cascade methodology on a fairly wide range of artificial model systems. Even so, there was only one example in the group of a cascade applied to a fragment of a ladder polyether: the synthesis of the *HIJK* ring system of gymnocin A.[1] We anticipated that exploration of a full natural target would uncover new aspects of water-promoted epoxide opening.

Our group is now working to construct a complete ladder polyether structure, that of the marine toxin gambierol (**1**), via *endo*-selective epoxide-opening cascades in water. The target was selected and our overall retrosynthetic strategy devised by Dr. Denise A. Colby.

Figure 1. Structure of gambierol.



gambierol (**1**)

The bioactivity of gambierol is interesting among ladder polyethers. Produced by the marine dinoflagellate *Gambierdiscus toxicus*, it was isolated relatively recently, with the first report of its structure disclosed in 1993 by Yasumoto and coworkers.[2] Along with the more lethal maitotoxin and ciguatoxins, gambierol is a likely contributor to

[1] Van Dyke, A. R.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 4430-4432.
[2] (a) Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361. (b) Morohashi, A.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *40*, 97.

devastating ciguatera poisoning.[2a,3] However, gambierol is probably only a minor contributor, as it evinces significant but not extreme toxicity, with a murine LD_{50} of 50 μg/kg.[2a]

It is not gambierol's toxicity but rather the target of its binding that makes it special. While the majority of ladder polyethers bind to voltage-gated sodium transport channels (Na_v channels) and induce persistent activation,[4] gambierol uniquely binds to voltage-gated potassium channels (K_v channels) and effects their inactivation.[5] Indeed, gambierol's affinity for the K_v channels in murine taste cells makes it one of the strongest binders known, with an IC_{50} of less than 2 nM.[5] Interestingly, gambierol is an antagonist for brevetoxin B and has been shown to inhibit the binding of BTX B to Na_v channels.[6]

Active investigation of the chemical biology of gambierol continues. For example, in 2009 the use of gambierol as a molecular probe revealed previously unknown binding sites in K_v channels.[5d] Most of the foregoing studies have tested synthetic samples of gambierol, as vanishingly small quantities have been isolated from nature.[7] Total synthesis therefore remains the best avenue for generating sufficient material for further structure-activity relationship (SAR) studies.

B. Structural analysis and review of total syntheses of gambierol.

Total synthesis of a target of gambierol's complexity is a major undertaking. Gambierol is an octacyclic ladder polyether composed of six six-membered tetrahydropyran (THP) rings and two seven-membered oxepanes, one of which is

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[3] (a) Nicholson, G. M.; Lewis, R. J. *Marine Drugs* **2006**, *4*, 82-118. (b) Fuwa, H.; Kainuma, H.; Satake, M.; Sasaki, M. *Biorg. Med. Chem. Lett.* **2003**, *13*, 2519. (c) Ito, E.; Suzuki-Toyota, F.; Tashimori, K.; Fuwa, H.; Tachibana, K.; Satake, M.; Sasaki, M. *Toxicon,* **2003**, *42*, 733. (d) Fuwa, H.; Kainuma, K.; Tachibana, K.; Tsukano, C.; Satake, M.; Sasaki, M. *Chem. Eur. J.* **2004**, *10*, 4894.

[4] (a) Kobayashi, J.; Ishibashi, M. Marine Natural Products and Marine Chemical Ecology. In *Comprehensive Natural Product Chemistry*; Baron, D.; Nakanishi, K., Eds.; Elsevier: New York, 1999; 476-515. (b) Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7182-7225.

[5] (a) Ghiaroni, V.; Sasaki, M.; Fuwa, H.; Rossini, G. P.; Scalera, G.; Yasumoto, T.; Pietra, P.; Bigiani, A. *Toxicol. Sci.* **2005**, *85*, 657-665. (b) Cuypers, E.; Abdel-Mottaleb, Y.; Kopljar, I.; Rainier, J. D.; Raes, A. L.; Snyders, D. J. *Toxicon,* **2008**, *51*, 974. (c) Pietra, F. *J. Phys. Org. Chem.* **2008**, *21*, 997-1001. (d) Kopljar, I.; Labro, A. J.; Cuypers, E.; Johnson, H. W. B.; Rainier, J. D.; Tytgat, J.; Snyders, D. J. *Proc. Natl. Acad. Sci.* **2009**, *106*, 9896-9901.

[6] Inoue, M.; Hirama, M.; Satake, M.; Sugiyama, K.; Yasumoto, T. *Toxicon* **2003**, *41*, 469.

[7] Yasumoto and coworkers describe collecting about 1 mg of gambierol from 1100 L of dinoflagellate fermentation broth in their original isolation report; see ref. 2a.

unsaturated. In total, the structure encompasses 18 stereogenic centers. The topography of the ladder is of the canonical *trans-syn-trans* variety.

Nonetheless, four impressive total syntheses of gambierol have been reported to date, from Sasaki,[8] Y. Yamamoto,[9] Rainier,[10] and Mori.[11] The syntheses of Sasaki, Yamamoto, and Rainier were comprehensively reviewed by Nakata in 2005,[12] and we will not recapitulate any of them in great detail. However, we must briefly highlight some of the distinct and creative approaches to THP and oxepane formation applied in these four syntheses. Among the methods used are an ingenious SmI_2-mediated reductive cyclization protocol (a technique pioneered by the Nakata group[13]) applied in the syntheses of Sasaki and Yamamoto and a Ti-mediated ring closing metathesis on an unusual enol ether substrate in Rainier's. Moreover, the syntheses of Sasaki, Yamamoto, and Mori each incorporate multiple *endo*-selective epoxide-opening cyclization steps. In the Sasaki and Yamamoto syntheses, these cyclizations involve attack of an alcohol onto an epoxide bearing a vinyl directing group, in an application of the tactic developed by Nicolaou.[14] Remarkably, Mori forms seven of gambierol's eight rings via *endo*-selective cyclization onto sulfonyl-substituted epoxides, using his group's methodology.[15] All of the above cyclization reactions are not cascade reactions but rather openings of a single epoxide, to form one cyclic ether at time. Rings are iteratively constructed and then, in the syntheses of Sasaki, Yamamoto, and Rainier, joined across the *D* and *E* rings to complete the ladder.

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[8] (a) Fuwa, H.; Sasaki, M.; Satake, M.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2981. (b) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 12983.

[9] (a) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46. (b) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Satake, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 11893.

[10] (a) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc.* **2005**, *127*, 848. (b) Majumder, U.; Cox, J. M.; Johnson, H. W. B.; Rainier, J. D. *Chem. Eur. J.* **2006**, *12*, 1736. (c) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *Chem. Eur. J.* **2006**, *12*, 1747.

[11] (a) Furuta, H.; Hasegawa, Y.; Mori, Y. *Org. Lett.* **2009**, *11*, 4382. (b) Furuta, H.; Hasegawa, Y.; Hase, M.; Mori, Y. *Chem. Eur. J.* **2010**, *16*, 7586. (c) Furuta, H.; Hase, M.; Noyori, R.; Mori, Y. *Org. Lett.* **2005**, *7*, 4061.

[12] Nakata, T. *Chem. Rev.* **2005**, *105*, 4314.

[13] Hori, N.; Matusukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron* **2002**, *58*, 1853., and references therein.

[14] (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. K.; Somers, P. K. *Chem. Commun.* **1985**, 1359. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (c) Nicolaou, K. C. *Angew. Chem. Int. Ed.* **1996**, *35*, 588.

[15] (a) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158. (b) Furuta, H.; Takase, T.; Hayashi, H.; Noyori, R.; Mori, Y. *Tetrahedron* **2003**, *59*, 9767.

C. Retrosynthetic analysis of gambierol. Proposed synthesis of gambierol via two epoxide-opening cascades promoted by water.

Of the four published total synthesis, that of Rainier and coworkers is shortest, at an admirably brief 44 steps from commercial starting materials to the natural product in the longest linear sequence and approximately 73 total synthetic operations. We aspired to realize a yet more rapid and efficient synthesis of gambierol. Inspired by the dramatic cascades of many epoxide openings that crown the proposed biosyntheses of the ladder polyethers,[16] we envisioned that incorporation of water-promoted epoxide-opening cascade reactions might enable considerably more rapid and efficient access to the natural product. Cascade reactions, of course, are capable of streamlining synthesis significantly, by compressing multiple elementary reactions into a single operation.[17] Alternatively referred to as domino reactions, their advantages include improved step economy and atom economy as well as consequent reduced waste generation.

Our specific strategy toward gambierol was initially conceived by Dr. Denise Colby. In broad terms, we planned a convergent synthesis substantially similar to those of Yamamoto and Rainier, one that disconnects gambierol's octacyclic core across its central *E* ring. Splitting the natural product so breaks its synthesis down to the formation of two smaller ladder subunits, the *ABCD* and the *FGH* ring systems (**2** and **3**, respectively, Scheme 1). We hypothesized that each subunit could, in turn, be derived from water-promoted, *endo*-selective epoxide-opening cascades of triepoxides **4** and **12**.

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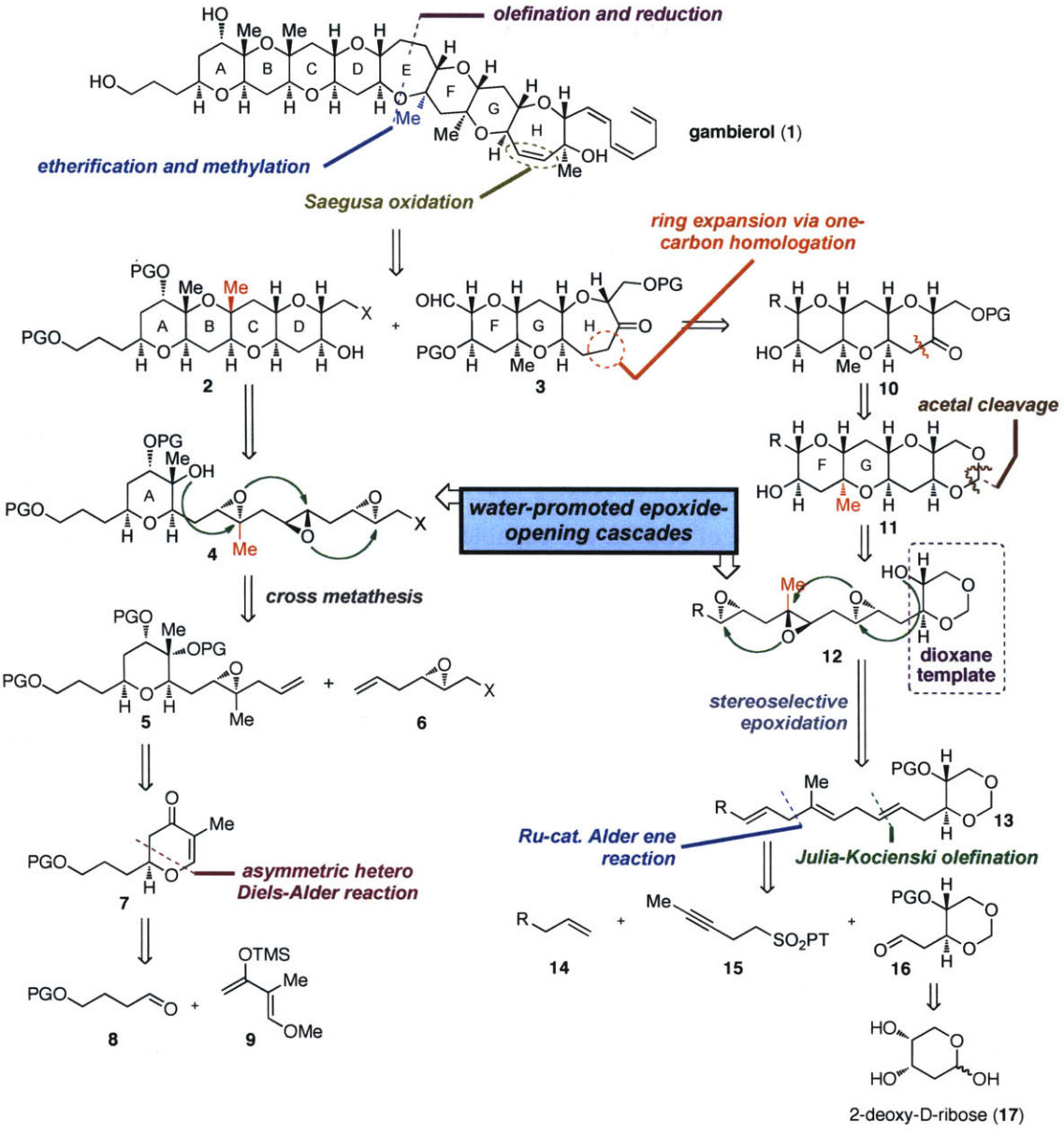
[16] Gallimore, A. R. *Nat. Prod. Rep.* **2009**, *26*, 266.

[17] For reviews, please see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, 45, 7134. (c) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (d) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, 2, 167.

Scheme 1. Retrosynthetic analysis of gambierol (**1**).

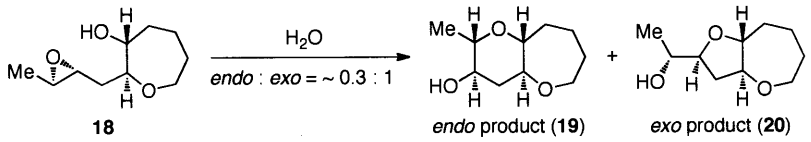


The formation of medium rings, either seven- or eight-membered, via *endo* epoxide opening remains a major outstanding challenge in the group and a topic of active research. The approach to gambierol outlined above enabled us to sidestep the direct formation of seven-membered rings in a cascade. We envisioned that the *E* ring oxepane would be generated in the course of fragment coupling. Specifically, an olefination and reduction sequence would form the C—C bond at the top of the ring, and a

methylation/etherification step would then close the *E* ring and concomitantly install the axial Me group at the *EF* ring junction.

The second medium ring is the oxepene H ring. Preliminary investigation by others in our group had suggested that seven-membered rings are inadequate templates for THP formation via 6-*endo* epoxide-opening cyclization (Scheme 2).[18]

Scheme 2. Water-promoted epoxide-opening cyclization with an oxepane template (Byers, Vilotijevic, and Jamison, ref. 18).



We therefore chose not to use the *H* ring as a template for a cascade to generate the *FGH* system. Instead, we imagined generating the *H* ring of **3** through a one-carbon ring expansion of tetrahydropyranone **10**. The one-carbon homologation of tetrahydropyranones by insertion of TMS-diazomethane through a Tiffeneau-Demjanov-type rearrangement is well-precedented[19] and indeed has been applied before to generate the *H* ring of gambierol, in the total synthesis by Mori.[11a]

Tetrahydropyranone **10** can then be traced back to tetracycle **11** through simple cleavage of the methylene acetal ring and oxidation. The methylene acetal of **11** is a key component; it was selected for its aptitude as a template for *endo*-selective epoxide-opening cyclization (see Chapter IV for extended discussion). Tetracycles **2** and **11** are thus traced in turn to **4** and **12**, respectively, through cascades of *endo* epoxide opening. Both **4** and **12** incorporate a mixture of both *trans*-disubstituted and trisubstituted epoxides, making them good candidates for cascades promoted by water (see Chapter II). We note that the two cascades were set up to run in opposite directions (i.e., that of **4** from left to right and that of **12** from right to left) so as to incorporate the more benign distal Me substitution pattern rather than challenging proximal Me substituents (distal Me substituents shown in red in Scheme 1; see Chapter II). We anticipated that the highly

[18] Byers, J. A.; Vilotijevic, I.; Jamison, T. F. *Manuscript in preparation.*
[19] (a) Hashimoto, N.; Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 119. (b) Mori, Y.; Yaegashi, K.; Furukawa, H. *Tetrahedron* **1997**, *53*, 12917.

robust methylene acetal of **12** would survive the elevated temperature and long reaction time required to drive the cascade reaction to completion (see Chapter IV).

Furthermore, the "capping" substituents X and R at the end of each triepoxide chain in substrates **4** and **12** needed also to be durable enough to survive the conditions of cascade reaction. These same groups must later be converted into appropriate synthetic handles for fragment coupling and *E* ring synthesis. We eventually discovered that selection of a suitable capping group for triepoxide **12** is essential, as the identity of R has a powerful effect on the efficiency of the cascade itself.

Triepoxide **4** could be dissected via retrosynthetic analysis into simpler epoxides **5** and **6** via cross metathesis. The stereochemically dense THP ring of **5** would ultimately be derived from dihydropyranone **7**, the product of an asymmetric hetero Diels-Alder reaction between aldehyde **8** and diene **9**.[20]

Toward the *FGH* fragment, triepoxide **12** could arise from diastereoselective epoxidation of **13**, most probably using Shi's protocol.[21] Skipped triene **13** would in turn be assembled after a ruthenium-catalyzed Alder ene reaction[22] between alkene **14** and alkyne **15** followed by Julia-Kocienski olefination[23] with aldehyde **16**. Finally, aldehydes of the form **16**, containing a detachable 1,3-dioxane template, are readily accessible from 2-deoxy-D-ribose (**17**), a cheap chiral pool starting material.[24]

The synthesis of the *ABCD* system was undertaken by Dr. Denise Colby in our group. Early work on the *FGH* system was carried out by Dr. Aaron R. Van Dyke, who initially demonstrated the feasibility of a water-promoted *endo*-selective cascade of two epoxide openings templated by a methylene acetal (Scheme 3).[25] Dr. Van Dyke also first outlined the route to the *FGH* system described above, a more ambitious cascade of three epoxide openings to be followed by ring expansion. This strategy has proved fruitful.

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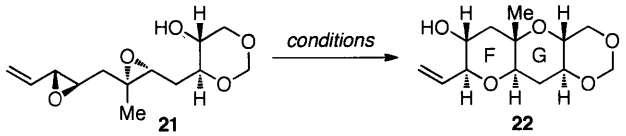
[20] Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398.
[21] (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.
[22] (a) Trost, B. M.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 4361. (b) Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. (c) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739. (d) Trost, B. M.; Machacek, M.; Schnaderback, M. J. *Org. Lett.* **2000**, *2*, 1761.
[23] Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.
[24] (a) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, C.; Hwang, C. K. *Tetrahedron* **1990**, *46*, 4517. (b) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019. (c) Inoue, M.; Wang, J.; Wang, G.-X.; Ogasawara, Y.; Hirama, M. *Tetrahedron* **2003**, *59*, 5645.
[25] Van Dyke, A. R. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 2009.

Scheme 3. Two-epoxide cascade to the *FG* rings of gambierol (Van Dyke and Jamison, ref. 25).

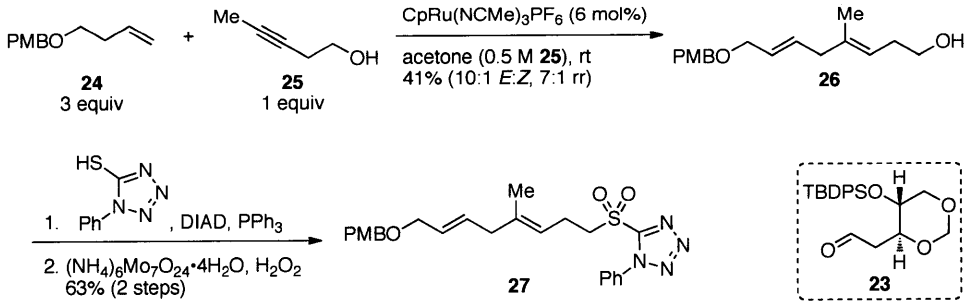


conditions:	*yield 22*:
CSA (cat.), CH_2Cl_2, rt	65%
H_2O, 60 °C	25%

D. Progress toward the *FGH* system, part 1: Cascades with a *p*-methylbenzyloxy (PMBO) cap.

We commenced with the synthesis of a skipped triene of the form **13** (Scheme 1). With aldehyde **23** in hand (see Chapter IV for its preparation), our attention turned to the synthesis of a sulfone partner for Julia-Kocienski olefination. The Kocienski-modified Julia reaction was chosen over other common olefination reactions for its high *E* selectivity.[23] We initially targeted skipped diene/*N*-phenyl tetrazole sulfone **27** (Scheme 4), capped by a *p*-methoxybenzyl (PMB) ether, a protecting group selected for its orthogonality to other protecting groups planned later in the synthesis.

Scheme 4. Synthesis of skipped diene sulfone partner for Julia-Kocienski olefination. (For the preparation of **23**, please see Chapter IV.)



To generate the requisite skipped diene motif we turned to Trost's Ru-catalyzed formal Alder ene reaction,[22] an implementation first suggested by Dr. Denise Colby. This

straightforward transformation enables the generation of relatively complex skipped diene products from simple alkene and alkyne starting materials with good regio- and stereoselectivity. PMB-protected homoallyl alcohol (**24**)[26] and 3-pentyn-1-ol (**25**) were reacted with a cationic ruthenium catalyst, $CpRu(NCMe)_3PF_6$, to afford skipped diene **26** (Scheme 4). The high regioselectivity in favor of the desired linear diene rather than the branched isomer is attributed to the coordinative ability of the Lewis basic hydroxyl substituent of **25**.[27] While the reaction proceeded cleanly, its Achilles heel proved to be the instability of the catalyst, which decomposed under the reaction conditions. To reach full conversion of **25**, catalyst loadings of 10-15 mol% were necessary — impractical, given the cost of $CpRu(NCMe)_3PF_6$, which at approximately $350/g was by far the most expensive component. Thus the reaction conditions were initially optimized to achieve a compromise between conversion and catalyst consumption, with 6 mol% found best. Later, Dr. Alicia Gutierrez in our group developed a cost-effective process for multigram-scale production of $CpRu(NCMe)_3PF_6$.[28] Additionally, improved reaction conditions and a modified substrate pairing later enabled nearly complete conversion at catalyst loadings near 5 mol% (*vide infra*).

The primary alcohol of **26** was then displaced by 1-phenyltetrazole-5-thiol in a Mitsunobu reaction,[29] and the resulting sulfide was oxidized under conditions selective for sulfur,[30] leaving the skipped diene intact in sulfone **27** (Scheme 4).

With sulfone **27** and aldehyde **23** in hand, the stage was set for Julia-Kocienski[23] olefination. Gratifyingly, the reaction proceeded smoothly to give skipped triene **28** (Scheme 5). The use of DMPU as cosolvent with THF was necessary to induce high *E* selectivity in the formation of the new olefin.[31]

Triene **28** was then epoxidized under Shi's protocol.[21] We planned to install all three epoxides in a single operation. Recognizing that the allylic ether of **28** is rather

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[26] Compound **24** can be synthesized in one step from 3-buten-1-ol; see Gupta, P.; Kumar, P. *Eur. J. Org. Chem.* **2008**, *7*, 1195.

[27] (a) Trost, B. M.; Müller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888. (b) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396.

[28] Gutierrez, A. C.; Jamison, T. F. *J. Flow Chem. submitted.*

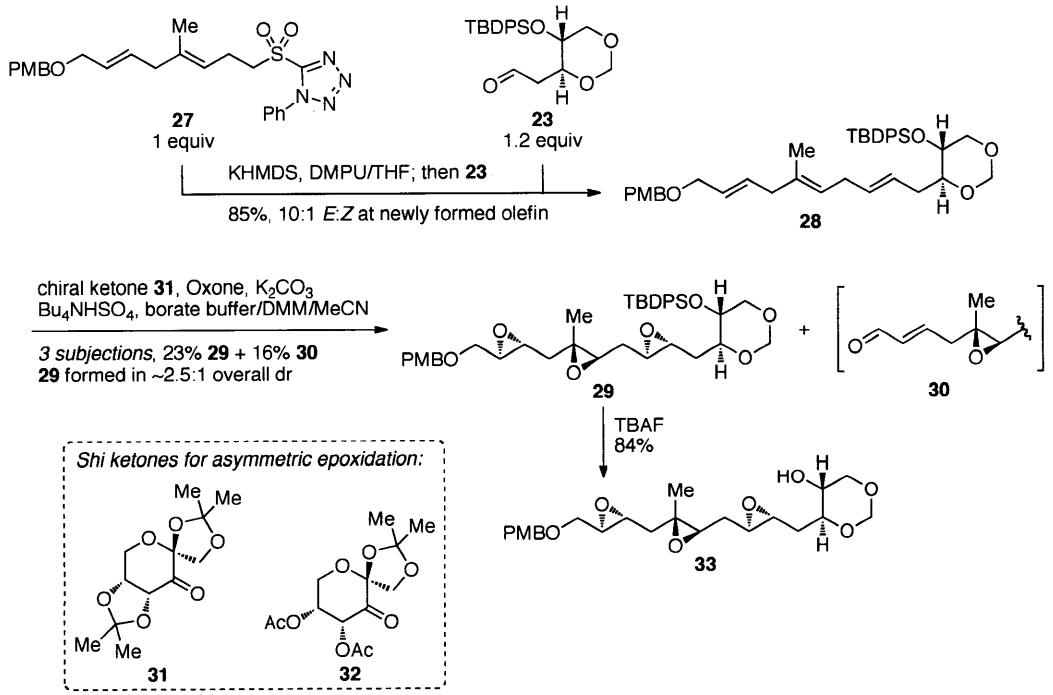
[29] For reviews of the Mitsunobu reaction, please see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Kumara Swamy, K. C.; Bhuvan Kumar, N. N.; Balaraman, E.; Pavan Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 2551.

[30] (a) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Am. Chem. Soc.* **1963**, *28*, 1140. (b) Smith, A. B., III, Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102.

[31] Pospíšil, J. *Tetrahedron Lett.* **2011**, *52*, 2348.

electron poor and therefore likely to be sluggish under standard Shi conditions, we initially applied the highly electrophilic and reactive dioxirane reagent derived from chiral diacetate ketone **32**.[32] Disappointingly, it led to very low yields of the desired triepoxide **29** and instead to formation of an undesired side product, assigned as enal **30**. This is less remarkable in retrospect, as strongly electrophilic dioxiranes have been reported to effect oxidative cleavage of PMB ethers.[33] The liberated allylic alcohol may then go on to react further to give enal **30**. Somewhat better yields of **29** were obtained after multiple rounds of reaction with the standard Shi ketone **31**. However, incomplete reaction of the allylic ether was observed even after three subjections, and enal **30** remained a significant side product. Clearly the PMB ether of **28** was not suitable for this transformation.

Scheme 5. Synthesis of PMB-capped triepoxide cascade substrate.



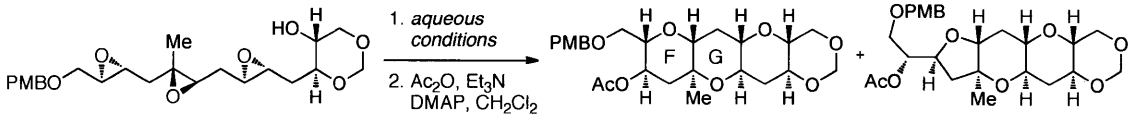
[32] Wang, B.; Wu, X.-Y.; Wong, O. A.; Nettles, B.; Zhao, M.-X.; Chen, D.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 3986.

[33] Paquette, L. A.; Kreilein, M. M.; Bedore, M. W.; Friedrich, D. *Org. Lett.* **2005**, *7*, 4665.

We proceeded to cleave the silyl ether of **29** to provide triepoxy alcohol **33**. Exploration of the reaction of **33** in water soon revealed an additional problem with the *p*-methylbenzyloxy substituent capping the epoxide chain.

As expected, the water-promoted cascade reaction of dioxane-templated **33** was much slower than similar cascades initiated by a THP-templated alcohol. Observation of the disappearance of **33** in D_2O indicated only about 50% consumption after three days at 70 °C. Indeed, heating to 70 °C for 14 days or longer proved necessary to achieve full conversion. After acetylation of the crude cascade mixture (to facilitate analysis by ^1H NMR and purification), two major products were identified: the desired tetrad **34** and 5,6,6,6-fused tetracycle **35** (Table 1).

Table 1. Reactions of PMB-capped triepoxide **33** in aqueous solution.



33 3:1 overall dr **34** **35**

entry	solvent[a]	T (°C)	*t*	yield **34**[b]	yield **35**[b]
1	deionized H_2O	70	17 d	28%	25%
2	0.1 M KP_i, pH 6.0	70	17 d	33%	27%
3	0.1 M KP_i, pH 7.0	70	17 d	30%	25%
4	0.1 M KP_i, pH 8.0	70	17 d	15%	19%

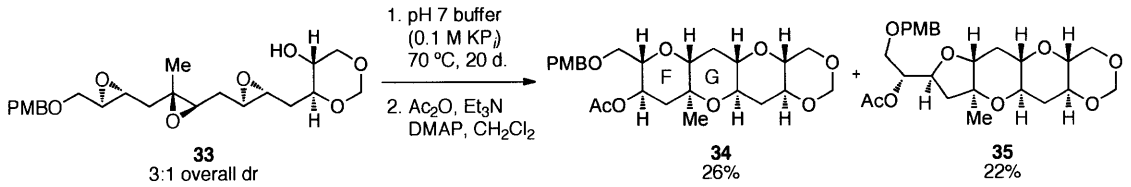
[a] All reactions were carried out at 0.02 M and taken to >98% conversion of **33**. [b] NMR yields.

Additional side products were also detected in each case, but these could not be isolated cleanly. All were significantly more polar than **34** and **35**, suggesting at least one epoxide opening by hydrolysis. Some of these likely arise from minor diastereomers of **33**.

Deionized water (entry 1) and potassium phosphate buffer at pH 6 and 7 (entries 2 and 3) all gave similar results, with approximately 30% yields of tetrad **34** and nearly equal quantities of *exo* product **35**. The undesired **35** predominated over **34** at pH 8 (entry 4). Promotion of the cascade with acids in organic solvent (either $BF_3 \cdot OEt_2$ or CSA in CH_2Cl_2) produced intractable mixtures, with no apparent trace of **34**.

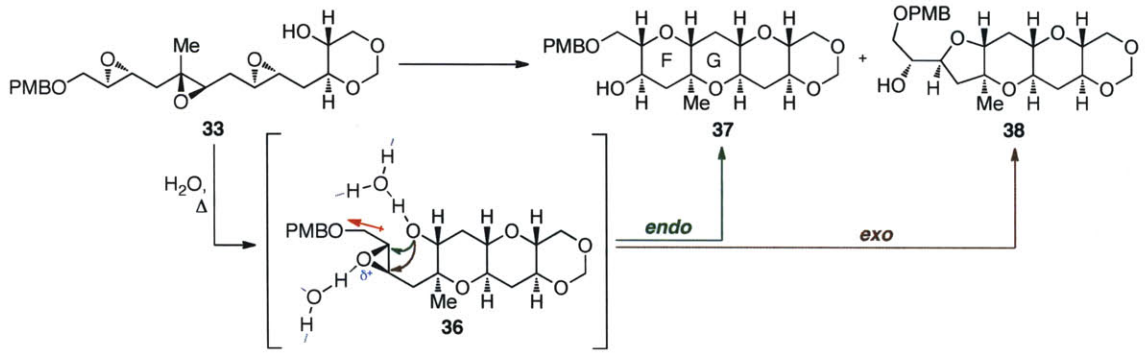
The reaction of **33** in deionized water was reproduced on preparative scale, and after acetylation gave **34** and **35** in 26% and 22% isolated yields, respectively (average of two experiments, Scheme 6).

Scheme 6. Cascade reaction of **33** and isolated yields of tetracycles **34** and **35**.



Our results in water imply a low regioselectivity of about 1:1 in the final epoxide-opening step of the cascade. To rationalize this phenomenon, we invoke an explanation introduced in Chapter III: an inductive electron withdrawing effect. Epoxy alcohol **36** is the ultimate intermediate along the presumed stepwise reaction pathway from **33** to tetrad **37** (Scheme 7). If the transition states for cyclization of **36** involves some epoxonium character, then the inductive electron-withdrawing effect of the *p*-methylbenzyloxy group could destabilize a partial positive charge at the *endo* site of attack, thereby discouraging opening at that site. Instead, more material would then be funneled through the *exo* pathway to **38**. A destabilizing effect should also slow down the rate of the cascade, which is consistent with the exceptionally long reaction time required for **33**. Moreover, Dr. Van Dyke in our group separately observed low reaction rates in the cascade reaction of a substrate capped by a PMB ether and was furthermore able to isolate a partially cyclized cascade intermediate similar to **36**.[1]

Scheme 7. Hypothesized inductive electron-withdrawing effect of PMBO- cap contributes to poor regioselectivity in the cascade reaction of **33**.



Of course, we must acknowledge that our group's investigation into the mechanism of epoxy alcohol cyclization has predominantly pointed to entropic factors dictating regioselectivity, not enthalpic.[18,34] An entropic explanation could also be invoked for eroded *endo* selectivity, one similar to that invoked in Chapter III. The PMB ether is not only electron withdrawing but also bulky. Its presence will undoubtedly perturb the shell of water molecules that surround the final epoxide in both its ground state and in the transition states to *endo* and *exo* cyclization, affecting $\Delta S^{\ddagger}$.

In any event, the preparation and reaction of **33** taught us of two serious problems associated with a *p*-methylbenzyloxy cap: first, a propensity to disintegrate during Shi asymmetric epoxidation, and second, a conjectured inductive electron-withdrawing effect that reduced selectivity in the key cascade reaction. We therefore contemplated switching to a capping substituent that might stabilize a neighboring carbocation, one that might actually reinforce *endo* selectivity in the last epoxide opening rather than undermine it.

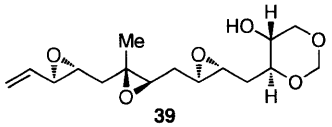
E. Progress toward the *FGH* system, part 2: Cascades with a vinyl cap.

To address low selectivity in the PMBO-capped cascade, we targeted a modified triepoxide substrate capped with a vinyl substituent. Epoxides bearing alkenyl substituents at their *endo* sites of attack have been used to great effect in *endo*-selective cascades, including examples from the groups of Nicolaou,[14] Nakata,[35] and McDonald[36]

[34] Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383.
[35] Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545.
[36] Valentine, J. C.; McDonald, F. E. *Synlett* **2006**, 1816.

(see Chapter I for more information). Especially appealing and straightforward to install was a simple vinyl group. Vinyl substituents to induce *endo* opening in epoxide-opening cyclizations were first introduced by Nicolaou in 1985[14] and have been applied widely in total synthesis since. Cyclizations of vinyl-substituted epoxides in water had not been described outside of Dr. Aaron Van Dyke's exploratory cascade of two epoxides (Scheme 3),[37] but we expected that the simple α-olefin would easily survive extended heating in water. Furthermore, after the cascade and ring expansion to generate the *FGH* system, a vinyl group could be ozonolyzed or otherwise converted to an aldehyde of the form **3** (Scheme 1). Thus our synthetic efforts toward a vinyl-capped triepoxy alcohol **39** commenced (Figure 2).

Figure 2. Vinyl-capped triepoxy alcohol **39**.



39

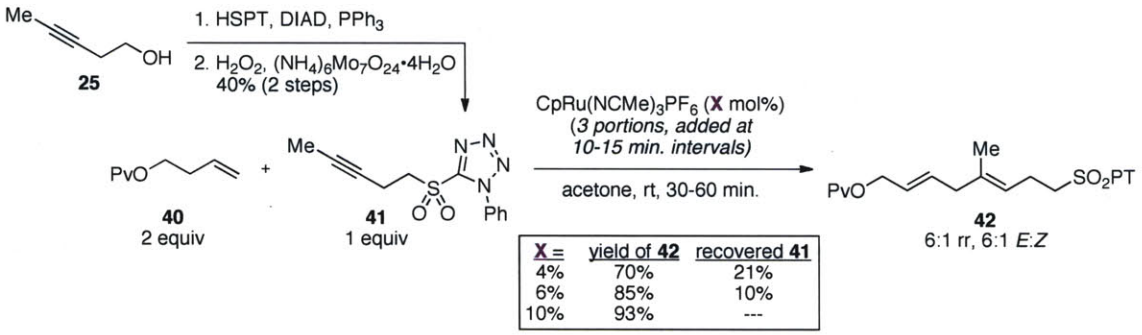
We conserved our retrosynthetic strategy in its broad outlines but revised its details in two respects. From the start, we replaced PMB-protected homoallyl alcohol **24** used with pivalate protected **40**, to evade issues of PMB instability during Shi epoxidation (Scheme 8). Secondly, reorganization of the sequence of steps before and after the Ru-cat. Alder ene reaction served to push this critical step later in the synthesis, thereby reducing somewhat the quantity of expensive $CpRu(NCMe)_3PF_6$ required.

Conversion of 3-pentyn-1-ol **25** to alkynyl sulfone **41** proceeded smoothly (Scheme 8). Alkyne **41** then proved an able substrate for the Alder ene reaction, reacting somewhat faster than **25** and therefore enabling the use of lower catalyst loadings. Good to excellent yields of skipped diene **42** were attained, even with 6 mol% $CpRu(NCMe)_3PF_6$. Three portionwise additions of the catalyst at intervals also improved efficiency. As before, we hypothesize that coordination of the appropriately positioned Lewis basic oxygens of **41** to the Ru catalyst is necessary to bias regioselectivity in favor

[37] While our work was ongoing, Nicolaou reported the use of neutral water as promoter for *endo* cyclization of a vinyl-substituted epoxide; see: Nicolaou, K. C.; Gelin, C. F.; Seo, J. H.; Huang, Z.; Umezawa, T. *J. Am. Chem. Soc.* **2010**, *132*, 9900.

of the desired linear product **42**. To the best of our knowledge, this reaction is the first example of a Ru-cat. Alder ene reaction on a substrate containing a sulfone.

Scheme 8. Synthesis of skipped diene sulfone **42**.



As before, Julia-Kocienski olefination of aldehyde **23** with sulfone **42** gave the requisite skipped triene **43** with acceptable yield and good stereoselectivity (Scheme 9). The pivalate ester of **42** was then cleaved with DIBALH and the triene epoxidized via Sharpless[38] and Shi[21] asymmetric epoxidations to give triepoxide **44**. In the latter case the more electrophilic and reactive chiral dioxirane reagent derived from a diacetate ketone **32** was found to afford better conversion and yield than the original **31**. While it was possible to effect complete epoxidation of all three alkenes using Shi's diacetate ketone catalyst, significant quantities of an enal side product arising from oxidation of the allylic alcohol were again observed, making the two-step sequence to **44** preferable. Cursory attempts to effect exhaustive Shi epoxidation directly on triene **43** were fruitless, as the allylic pivalate was unreactive.[39] Furthermore, even if epoxidation had succeeded, reductive cleavage of the pivalate ester in the presence of three epoxides would likely have proven challenging. In the event, with alcohol **44** in hand, subsequent Parikh-Doering oxidation[40] and methylenation via Wittig olefination provided alkene **45**. Finally, cleavage of the silyl ether of **45** provided triepoxy alcohol **39**, the substrate for cascade studies.

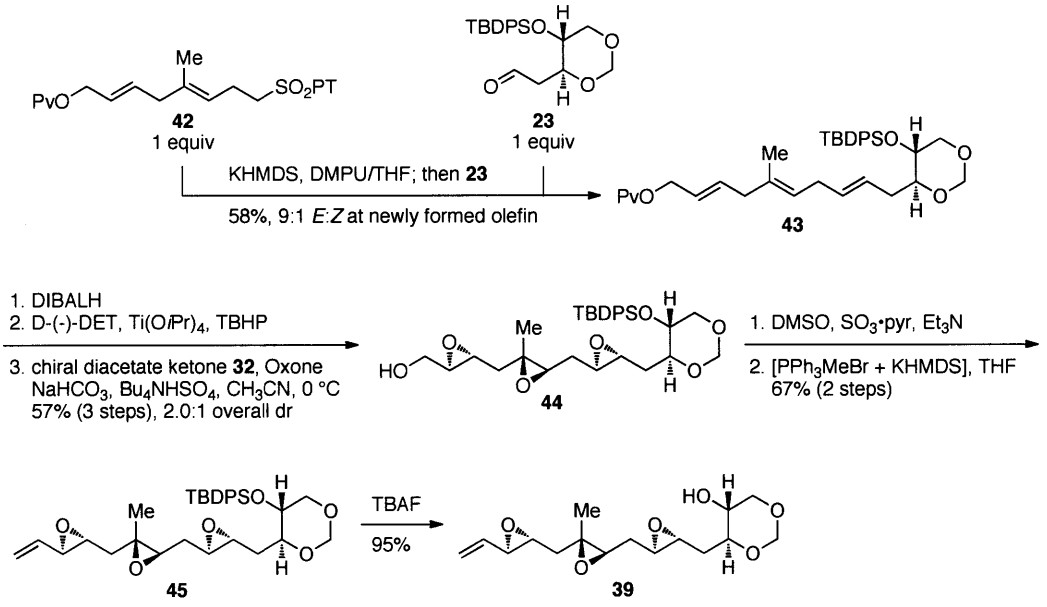
---

[38] *original references:* (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. *review:* (c) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

[39] Tong, R.; Boone, M. A.; McDonald, F. E. *J. Org. Chem.* **2009**, *74*, 8407.

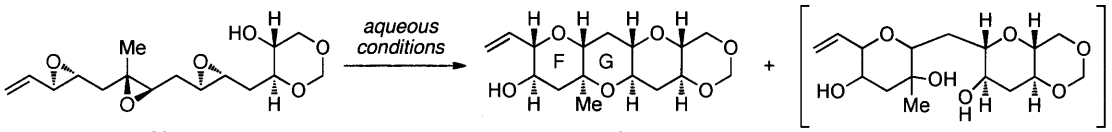
[40] Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

Scheme 9. Synthesis of triepoxy alcohol **39**.



We first investigated aqueous conditions for the cascade of triepoxide **39**. Immediately notable was the improved reaction rate of vinyl-capped **39** as compared to PMBO-capped **33**. On monitoring a cascade in D_2O at 70 °C by ^1H NMR, >98% conversion of **39** was observed after 6 days. However, while its rate was improved, the reaction proved otherwise disappointing. While some of the desired tetrad **46** was formed, the primary product of the reaction of **39** in neutral water was a triol, which could not be isolated cleanly. Its structure was tentatively assigned as **47** (Table 2). Compound **47** predominated in neutral water and at pH 6 (entries 1-3). At pH 8 (entry 4), only a trace of **47** was observed, but the yield of tetracycle **46** remained low at 22%.

Table 2. Reactions of vinyl-capped triepoxide **39** in aqueous solution.



39
4:1 overall dr

46

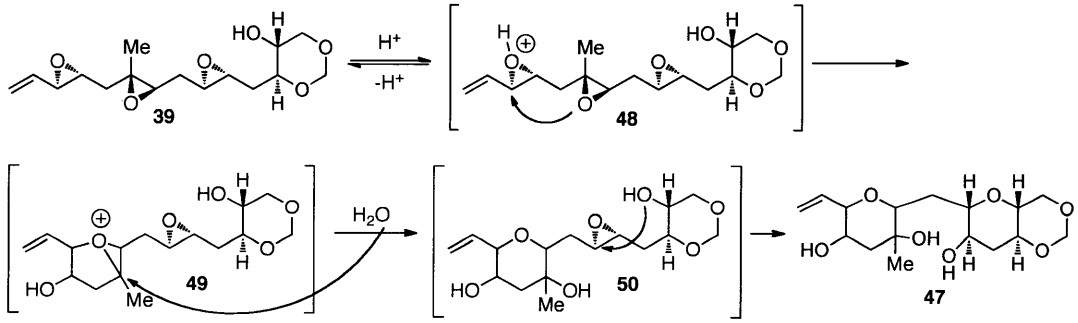
47

entry	solvent[a]	T (°C)	*t*	yield **46**[b]	yield **47**[b]
1	deionized H_2O	70	17 d	13%	~45%
2	0.1 M KP_i, pH 6.0	70	6 d	14%	~30%
3	0.1 M KP_i, pH 7.0	70	6 d	10%	~45%
4	0.1 M KP_i, pH 8.0	70	6 d	22%	<5%

[a] All reactions were carried out at 0.02 M and taken to >98% conversion of **39**. [b] NMR yields.

We hypothesize that **47** arises via an acid-promoted, electrophilic cascade mechanism (Scheme 10). The vinyl substituent of **39** stabilizes the neighboring carbocation, increasing the equilibrium concentration of epoxonium **48**. The vinyl substituent can then direct *endo* attack by the central epoxide, generating intermediate **49**. Finally, hydrolysis and subsequent *endo* opening of the remaining epoxide lead to **47**.

Scheme 10. Proposed acid-catalyzed mechanism for formation of **47**.

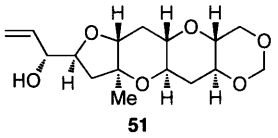


39 **48** **49** **50** **47**

In cascades of PMBO-capped triepoxide **33**, formation of *exo* tetrad **38** was the major side reaction pathway. In cascades of vinyl-capped **39**, we did not detect any *exo* tetrad (see **51,** Figure 3), which suggests that the vinyl group did indeed preserve the desired *endo* regioselectivity in the last epoxide-opening cyclization. This is entirely consistent with the work of Nicolaou and others, which demonstrates that vinyl substituents are potent directing groups that activate epoxides toward *endo* opening.[14] However, in our case, the vinyl capping group was found to be worse overall than the PMBO, as it proved *too* activating. Much as in the triepoxide cascade discussed in

Chapter II, we hypothesize that the presence of an epoxonium-stabilizing substituent on the last epoxide in the chain facilitates unproductive protonation and encourages initiation of cascades from the "wrong" end. The requisite stepwise, nucleophile-driven cascade initiated by the dioxane-templated alcohol is likely being outcompeted, and the result is low yield of the desired tetrad **46**.

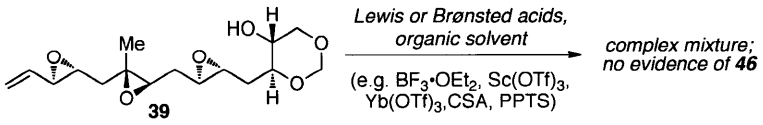
Figure 3. Vinyl-capped *exo* tetrad **51** (not observed).



51

Given our hypothesis that the vinyl-substituted epoxide of **39** was prone to activation by aqueous acid, we were curious about its behavior under other acidic conditions. The McDonald group, in particular, has demonstrated the viability of *endo*-selective cascades promoted by Lewis acids, even in a few cases where a central epoxide lacks a directing group.[41] However, reaction of **39** promoted by Brønsted and Lewis acids in organic solvents afforded intractable mixtures, with no evidence of the formation of tetrad **46** (Scheme 11).

Scheme 11. Unsuccessful cascade reactions of **39** promoted by Brønsted and Lewis acids.



39

To summarize, we found that a *deactivating* PMBO capping group harms the water-promoted cascade by eroding *endo* selectivity in the last cyclization, while an *activating* vinyl cap short-circuits the desired stepwise cascade and instead triggers an

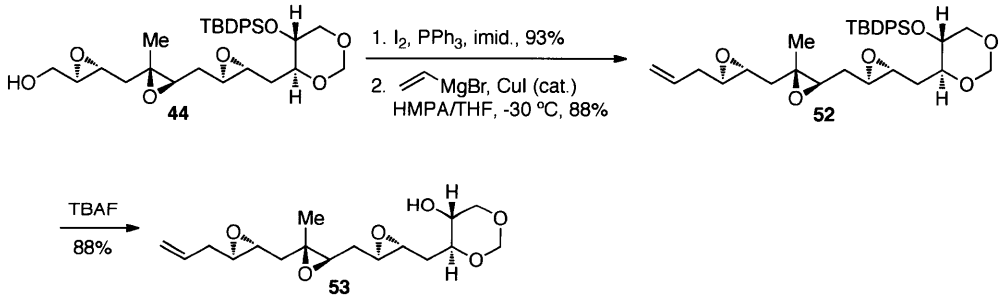
[41] *For selected original reports, see:* (a) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917. (b) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2003**, *5*, 2123. (c) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586. *For accounts, see:* (d) Valentine, J. C.; McDonald, F. E. *Synlett* **2006**, 1816. (e) McDonald, F. E.; Tong, R.; Valentine, J. C.; Bravo, F. *Pure Appl. Chem.* **2007**, *79*, 281.

acid-promoted side reaction. Thus it seemed that the ideal capping group might be the compromise, an electronically neutral one. Indeed, perhaps the simple methyl substituents that terminated our group's original model cascades were, coincidentally, the best possible choice. For the synthesis of gambierol, however, a Me cap is unsuitable, as we require a handle for fragment coupling.

F. Progress toward the *FGH* system, part 3: Cascades with an allyl cap.

We consequently turned to turned to allyl-capped substrate **53** (Scheme 12). As an intervening methylene prevents direct interaction of the π-system with the epoxide, the electronic effect of an allyl group were predicted to be similar to Me. However, oxidation, hydroboration, or other methods could be applied after the cascade to functionalize the alkene. We thus targeted allyl-capped triepoxide cascade substrate **53**, which was quickly generated in three steps from earlier intermediate **44** (Scheme 12).

Scheme 12. Synthesis of allyl-capped cascade substrate **53**.



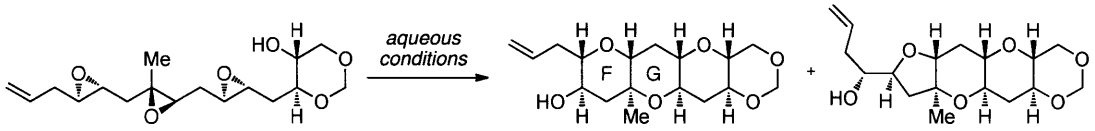
Primary alcohol **44** was smoothly converted to alkene **52** upon iodination[42] and subsequent displacement of the iodide with a vinyl cuprate reagent.[43] Desilylation of **52** then afforded triepoxy alcohol **53**.

Our first experiments with **53** were cascade reactions in D_2O observed by ^1H NMR. As predicted, these revealed that the rate of reaction of **53** was roughly intermediate between that of PMBO-capped **33** and vinyl-capped **39**, with >98%

[42] Mori, K.; Brevet, J.-L. *Synthesis* **1991**, 1125.
[43] Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Tetrahedron Lett.* **1984**, *25*, 2069.

conversion observed after heating to 70 °C for 14 days. Ultimately, we examined the reaction of **53** in water while varying buffer identity, temperature, and pH; the last two proved to have a strong impact on the efficiency of the desired cascade reaction (Table 3).

Table 3. Initial investigation of the cascade reaction of allyl-capped triepoxide **53** in aqueous solution.



53
2.5:1 overall dr

54

55

entry	solvent[a]	T (°C)	*t*	yield **54**[b]	yield **55**[b]
1	deionized H_2O	70	14 d	28%	4%
2	0.1 M PIPES, pH 7.0	70	14 d	29%	4%
3	0.1 M $NH_3/(NH_4)_2SO_4$	70	14 d	31%	3%
4	0.1 M KP_i, pH 6.0	70	14 d	29%	4%
5	0.1 M KP_i, pH 6.3	70	14 d	33%	5%
6	0.1 M KP_i, pH 6.6	70	14 d	30%	5%
7	0.1 M KP_i, pH 6.8	70	14 d	28%	4%
8	0.1 M KP_i, pH 7.0	70	14 d	28%	4%
9	0.1 M KP_i, pH 7.2	70	14 d	26%	4%
10	0.1 M KP_i, pH 7.5	70	14 d	23%	4%
11	0.1 M KP_i, pH 6.0	90	4 d	31%	4%
12	0.1 M KP_i, pH 6.1	90	4 d	33%	4%
13	0.1 M KP_i, pH 6.2	90	4 d	33%	3%
14	0.1 M KP_i, pH 6.3	90	4 d	31%	3%
15	0.1 M KP_i, pH 6.4	90	4 d	31%	5%
16	0.1 M KP_i, pH 6.5	90	4 d	32%	4%
17	0.1 M KP_i, pH 6.6	90	4 d	31%	4%
18	0.1 M KP_i, pH 6.7	90	4 d	30%	4%
19	0.1 M KP_i, pH 6.8	90	4 d	31%	4%
20	0.1 M KP_i, pH 6.9	90	4 d	29%	4%
21	0.1 M KP_i, pH 7.0	110	2 d	25%	4%
22	0.1 M KP_i, pH 7.0	120[c]	24 h	24%	5%
23	0.1 M KP_i, pH 7.0	140[c]	12 h	25%	3%
24	0.1 M KP_i, pH 7.0	170[c]	1 h	22%	3%
25	0.1 M KP_i, pH 7.0	190[c]	20 min	19%	2%

[a] All reactions were carried out at 0.02 M and taken to >98% conversion of **53**. [b] NMR yields. [c] Microwave heating.

Initial results in deionized water (entry 1) were promising, as the yield of desired tetrad **54** was comparable to that obtained with PMBO-capped **33**, even with **53** in low

diastereopurity. Changing from deionized water to pH 7 water buffered with either PIPES, ammonia, or potassium sulfate had a negligible impact (entries 2, 3, and 8). However, a significant and intriguing dependence on pH was observed. Contrary to our expectations, the highest yield of **54** was obtained not at pH 7 but rather in slightly acidic solution, with pH 6.1-6.6 apparently best (entries 5, 6, and 12-17). This trend was reproducible on small scale and later corroborated in preparative experiments (*vide infra*).

As a two-week reaction time is undesirable, we hoped that higher temperature reactions would be feasible. Reaction at 90 °C furnished yields similar to those observed at 70 °C, but at higher temperatures the yield of **54** declined (Table 3, entries 21-25).

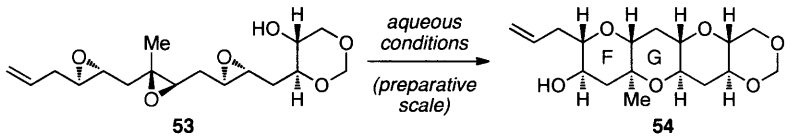
Cascade reactions of **53** provided complex mixtures of many products. The relative ratios of these products changed considerably with variation in pH and temperature. Only one of these compounds was successfully isolated and characterized: *exo* tetrad **55**. As before, we presume a stepwise mechanism for the formation of **54** and **55**. Therefore, the average ratio of **54**:**55** suggests that the final cyclization of the cascade proceeds with approximately 7:1 or 8:1 *endo* selectivity, a value that appears to hold from 70 to 190 °C and from pH 6 to pH 7.5.

We cannot currently present a compelling rationale for the intriguing observation that slightly acidic water is a better promoter than neutral water. From earlier studies, we would have predicted that reaction at pH 6 or even 6.5 would result in higher yields of side products formed from acid-promoted pathways and a commensurately lower yield of tetrad **54**. However, this is not the case. We showed in Chapter IV that dioxane-templated alcohols cyclize onto disubstituted epoxides under acidic promotion with good *endo* selectivity. Perhaps pH 6 or 6.5 is just acidic enough to activate the first epoxide in the chain to attack by the templated alcohol, thus successfully triggering the requisite stepwise cascade and allowing it to propagate. pH 6 and 6.5 are close enough to neutral that the neutral water-promoted pathway predominates in the second and third epoxide openings, and so good regioselectivity is maintained. This hypothesis assumes that the first cyclization in the cascade is the slowest of the three, something we have not yet confirmed experimentally.

In preparative experiments, tetrad **54** was cleanly isolated as a single diastereomer. We have prepared more than a gram of **54** via the water-promoted

cyclization of **53** (Table 4). In reactions on multigram scale (entries 1 and 2), triepoxide **53** appeared, superficially at least, to be fully soluble at 70 °C, dissolving to afford a clear solution. Reaction at pH 6.5 afforded a very slightly higher yield of **54** than pH 7.0. Samples of **53** in higher purity cyclized to **54** in better yield (entries 3 and 4). Adjusting for diastereopurity, **53** appears to cyclize in neutral or slightly acidic water in approximately 40-45% yield, or about 75% yield per ring formation.

Table 4. Preparative cascade reactions of **53**.



53 **54**

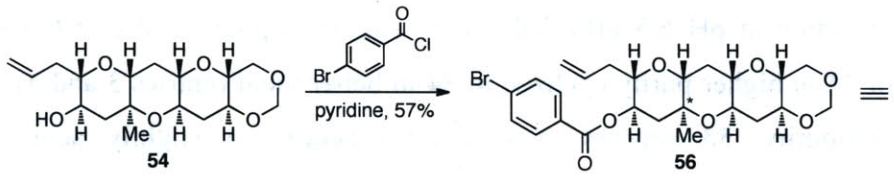
entry	overall dr of **53**	solvent[a]	T (°C)	*t*	isolated yield **54**	yield accounting for dr of **53**
1	2.0:1	0.1 M KP_i, pH 6.5	70	14 d	27%[b]	40%
2	2.0:1	0.1 M KP_i, pH 7.0	70	14 d	26%[c]	39%
3	4.4:1	0.1 M KP_i, pH 6.5	70	16 d	42%	51%
4	6.0:1	0.1 M KP_i, pH 6.5	70	15 d	40%	47%

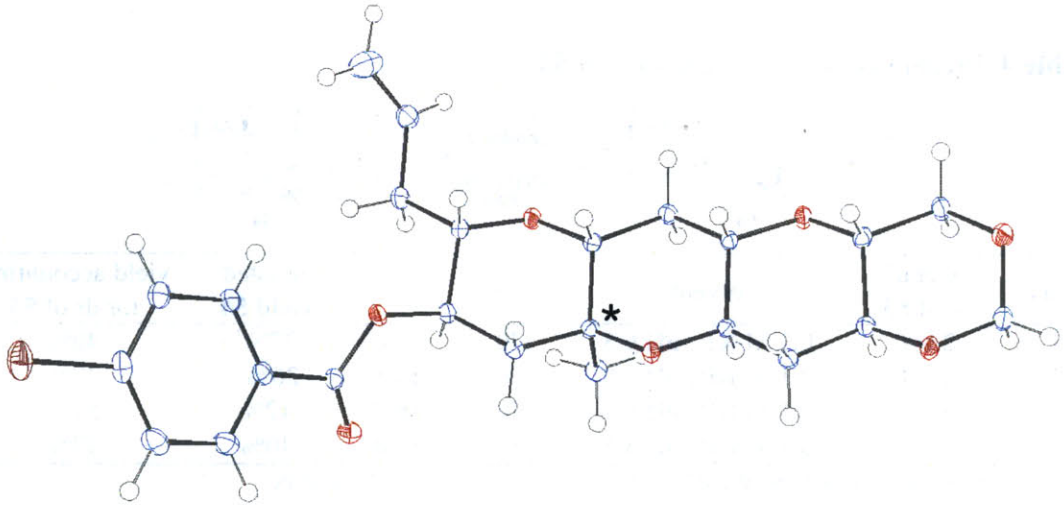
[a] All reactions were carried out at 0.020 or 0.025 M. [b] 2.0 g scale. [c] 2.7 g scale.

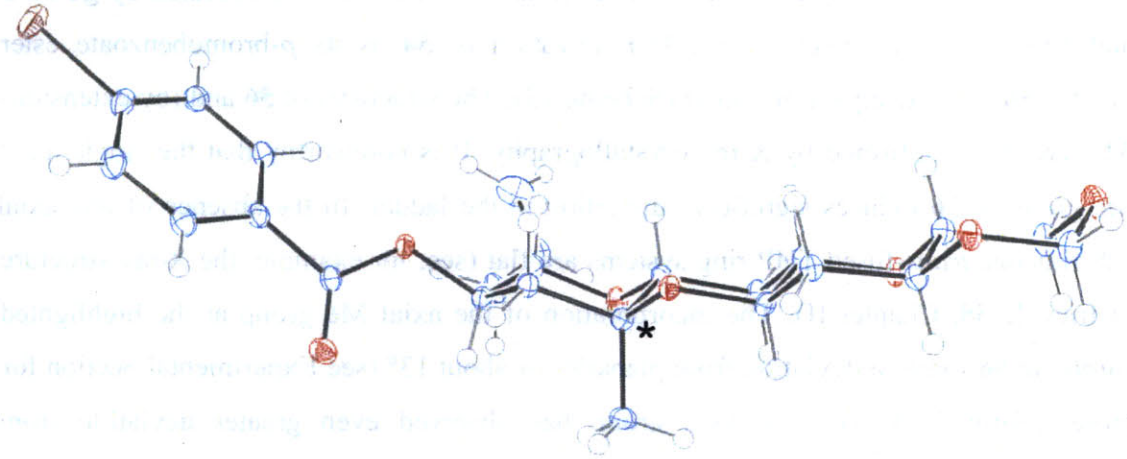
The connectivity and relative configuration of **54** were corroborated by gCOSY and NOESY NMR spectroscopy. Derivatization of **54** as its *p*-bromobenzoate ester yielded **56**, a white crystalline solid (Scheme 13). The structures of **56** and (by extension) **54** were then confirmed by X-ray crystallography. It is noteworthy that the single axial Me group in **56** induces significant distortion in the ladder. In the absence of any axial substituents, *trans*-fused THP ring systems are flat (see, for example, the X-ray structure of tricycle **38**, Chapter II). The incorporation of the axial Me group at the highlighted carbon in **56** forces a deviation from planarity of about 13° (see Experimental Section for more information). The Nicolaou group has observed even greater deviation from planarity in a fused THP system that incorporates axial Me groups at three neighboring ring junctions, thus triggering severe 1,3-diaxial interactions.[44]

[44] Nicolaou, K. C.; Seo, J. H.; Nakamura, T.; Aversa, R. J. *J. Am. Chem. Soc.* **2011**, *133*, 214.

Scheme 13. *p*-Bromobenzoate ester of allyl tetrad. (Crystal structures rendered with Ortep-3 for Windows v. 2.02.[45] Displacement ellipsoids are scaled to 50% probability.)







We venture that these deviations from planarity must destabilize the desired *endo* products and the transition states leading to them. This effect may explain why cascades

[45] Burnett, M. N.; Johnson, C. K. "ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustration," Oak Ridge National Laboratory Report ORNL-6895, 1996.
[47] Bailey, W. F.; Zarcone, L. M. J.; Rivera, A. D. *J. Org. Chem.* **1995**, *60*, 2532.

that contain trisubstituted epoxides generally proceed in lower yields than those built entirely of *trans*-disubstituted epoxides, even with the incorporation of the more favorable distal substitution pattern.

G. Ring expansion to provide the *FGH* ring system of gambierol.

With **54** in hand and the *F* and *G* rings of gambierol established, our attention turned to the generation of the *H* ring. To this end we executed our originally planned THP-to-oxepane ring expansion via Tiffeneau-Demjanov-type rearrangement (Scheme 14).[19] Alcohol **54** was protected as a TBDPS ether, and its methylene acetal was cleaved with zinc chloride and acetyl chloride to afford the primary acetate ester and secondary chloromethyl ether.[47] Workup with sodium methoxide then saponified the ester and displaced the chloride to provide MOM ether **57** in good yield.[48] Other methods for methylene acetal cleavage, including simple acidic hydrolysis, the commonly used TFAA/AcOH,[49] and mild deprotection with 2,2'-bipyridyl and a silyl triflate,[50] all gave low conversion in our hands. Free alcohol **57** was then protected as its PMB ether with PMB trichloracetimidate and catalytic CSA,[51] reagents that gave better conversion than NaH and PMBBr. The MOM ether was subsequently removed with PPTS in *t*BuOH, and the resulting 2° alcohol was oxidized with Dess-Martin periodinane[52] to furnish **55**, the substrate for ring expansion, in modest yield over three steps.

---

[48] Attempted reaction of the chloromethyl ether intermediate with MeOH and iPr$_2$EtN, as recommended in the procedure from Bailey and coworkers, gave very low conversion on our substrate.

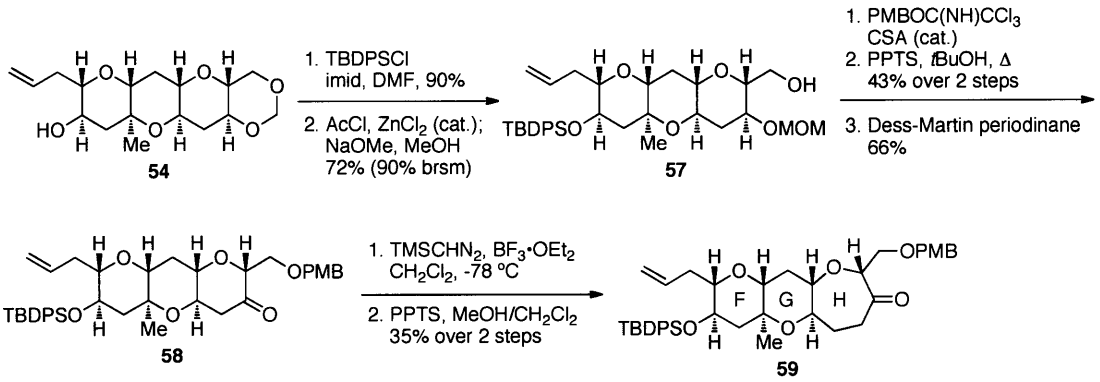
[49] (a) Bourne, E. J.; Burdon, J.; Tatlow, J. C. *J. Chem. Soc.* **1958**, 1274. (b) Gras, J.-L.; Pellissier, H.; Nouguier, R. *J. Org. Chem.* **1989**, *54*, 5675.

[50] (a) Fujioka, H.; Senami, K.; Kubo, O.; Yahata, K.; Minamitsuji, Y.; Maegawa, T. *Org. Lett.* **2009**, *11*, 5138. (b) Fujioka, H.; Senami, K.; Kubo, O.; Yahata, K.; Minamitsuji, Y.; Maegawa, T. *Chem. Pharm. Bull.* **2010**, *58*, 426.

[51] (a) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139. (b) Walkup, R. D.; Kane, R. R.; Boatman, D., Jr.; Cunningham, R. T. *Tetrahedron Lett.* **1990**, *31*, 7587.

[52] (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

Scheme 14. Ring expansion to the *FGH* ring system of gambierol.

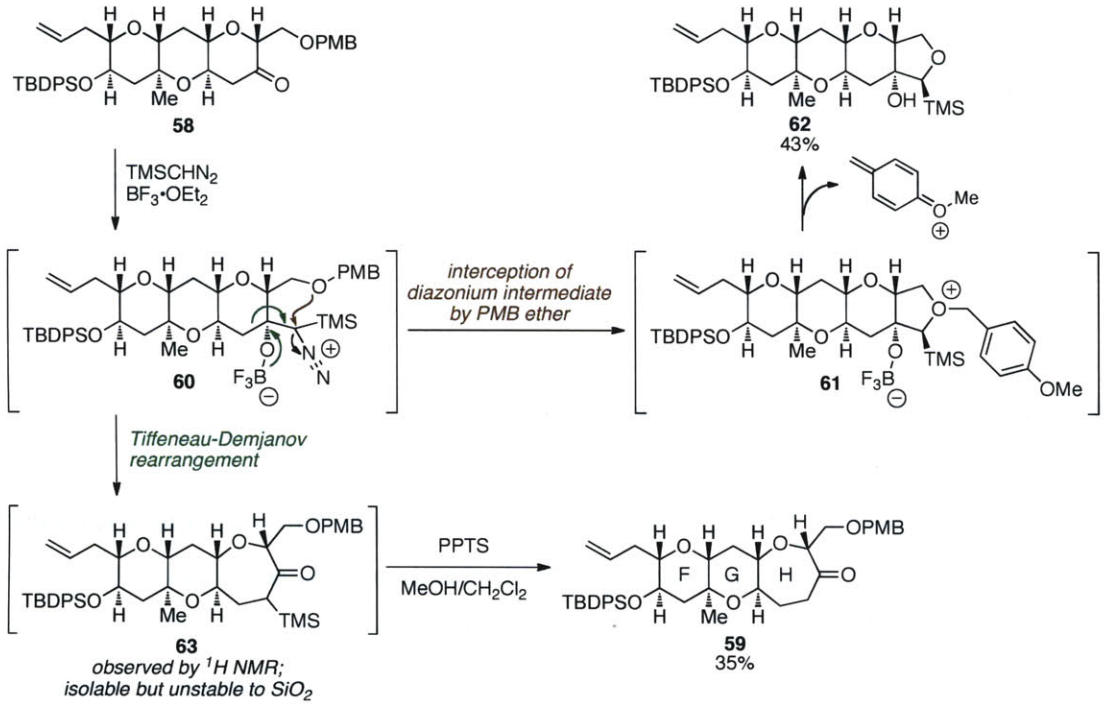


We were gratified to learn that ring expansion of **58** is a viable tactic for the construction of the *H* ring of gambierol. On activation of **58** with BF_3•OEt_2, $TMSCHN_2$ successfully added to the ketone, triggering a 1,2-alkyl shift and rearrangement to putative intermediate **63**, an α-silyl ketone (Scheme 15). Tautomerization and subsequent solvolysis of **63** with PPTS in MeOH then yielded oxepane **59** as a single regioisomer. The structure of **59** was corroborated by IR and by gCOSY, NOESY, and ^{13}C NMR (see Experimental Section).

While ketone **59** was cleanly obtained as a single regioisomer, the yield was disappointing. We were surprised to obtain only 35% of **59**, given the very close precedent for this two-step procedure from Mori's synthesis of gambierol.[11a] We attribute this to a side reaction pathway in which the PMB ether intercepts the initial diazonium intermediate to give THF **62**, which accounts for most of the missing mass (Scheme 15). Aoyama and Shioiri have previously shown that pendent free alcohols and TMS ethers can intercept the products of $TMSCHN_2$ addition to ketones, to generate dihydrofuran rings.[53] In Mori's synthesis, the neighboring primary alcohol is protected as a TBDPS ether, whose bulk presumably precludes it from attacking the diazonium intermediate.

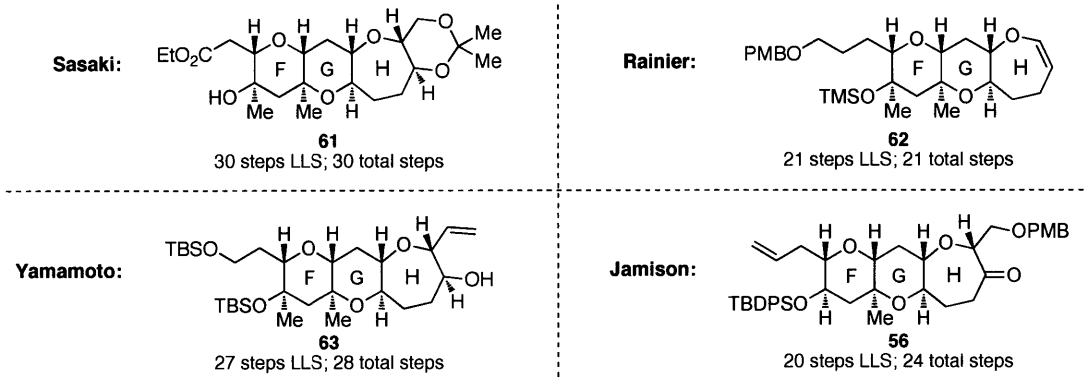
[53] Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 461.

Scheme 15. Hypothesized divergent reaction pathways after addition of $TMSCHN_2$ to ketone **58**.



An obvious and simple solution to the problem of **62** is the replacement of the PMB ether of **58** with another, bulkier protecting group. That work remains to be done, and **59** is the most advanced compound we have prepared. As it stands, we have completed a synthesis of the *FGH* ring system of gambierol in 24 total steps and in a 20 step longest linear sequence. This is considerably shorter than the approaches of Sasaki[8] and Yamamoto[9] to the *FGH* system, and comparable in overall efficiency to Rainier's route[10] (Figure 4).

Figure 4. Comparison of step counts in syntheses of the *FGH* rings of gambierol.

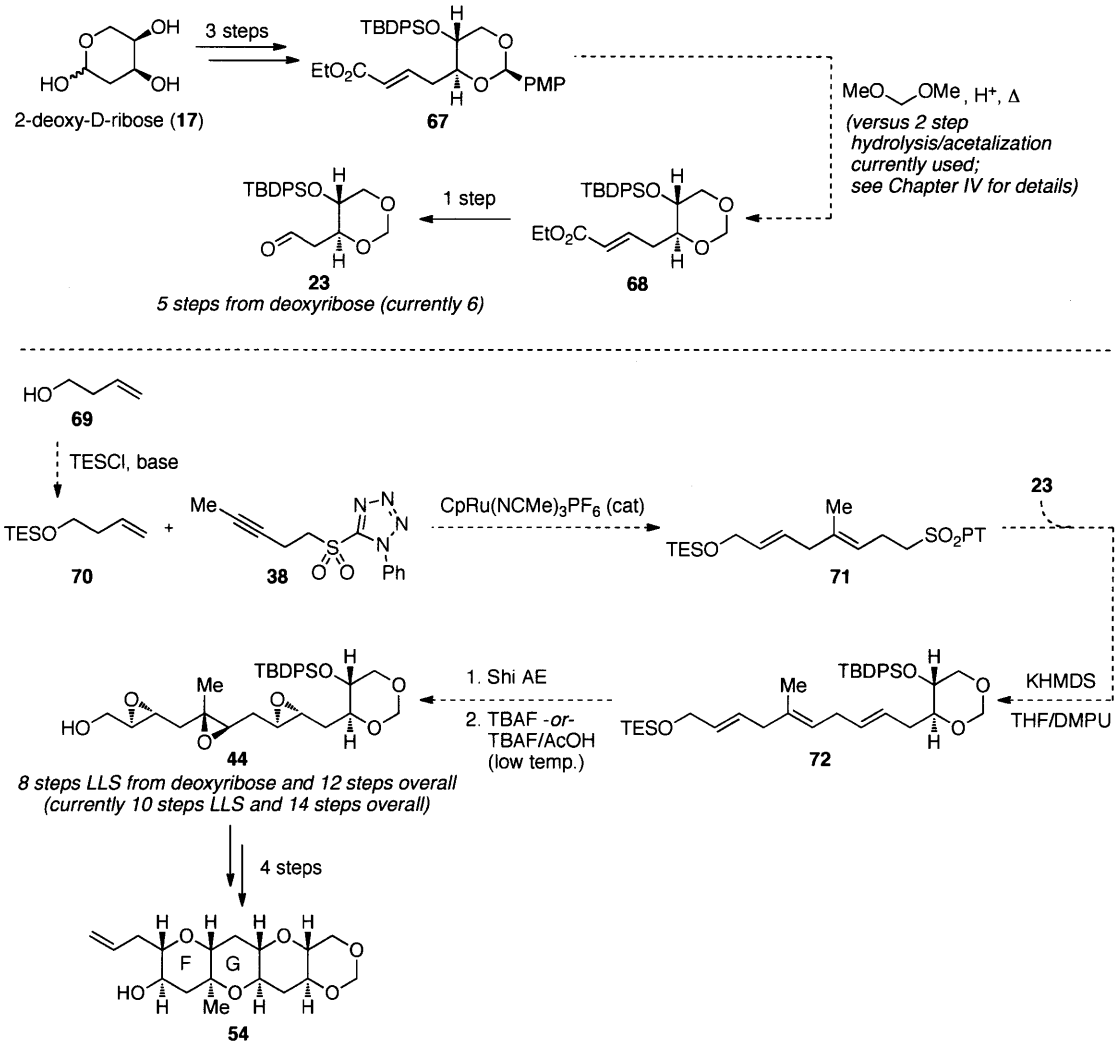


H. Proposed revised and streamlined synthesis of the *FGH* rings.

The synthesis of **59** could be streamlined somewhat with only minor revision to our overall approach. Specifically, we anticipate that two steps could easily be trimmed (Scheme 16). First, we currently install the methylene acetal ring of aldehyde **23** in two steps, from PMP acetal **67** to methylene acetal **68**. This procedure requires hydrolysis and subsequent reacetalization (see Chapter IV for the details of our current synthesis of **23**). The one-pot transacetalization of labile PMP acetals into more stable acetals using catalytic acid is known,[54] and application of this method would permit transformation of **67** into **68** in a single step. Second, we currently generate the three epoxides of intermediate **44** in a piecemeal fashion, via first Sharpless asymmetric epoxidation and then Shi epoxidation (Scheme 9). If the Ru-cat. Alder ene reaction began from triethylsilyl homoallyl ether **70**, then a sequence of steps otherwise identical to our current route would afford triene **72** (Scheme 16). Exhaustive Shi epoxidation should then be feasible, as allylic silyl ethers are competent substrates in Shi epoxidation.[21] Finally, we propose generating **44** through selective cleavage of the TES ether using TBAF at low temperature, which should not disturb the TBDPS ether.[55]

[54] (a) Shipe, W. D.; Sorenson, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 7025. (b) Das, S.; Abraham, S.; Sinha, S. C. *Org. Lett.* **2007**, *9*, 2273.
[55] Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833.

Scheme 16. Proposed streamlined synthesis of intermediate **44**.



I. Toward fragment coupling and completion of the synthesis.

From ketone **59** (or better a variant of **59** with an amended protecting group pattern) only a few steps are required to prepare the *FGH* rings for fragment coupling (Scheme 17). We plan protection of ketone **59** as a 1,3-dioxolane and subsequent selective one-bond isomerization of the alkene using a ruthenium hydride species derived from Grubbs 2nd generation catalyst **73**[56] to provide **74**. Ozonolysis of **74** will furnish

[56] For selective and mild one-bond isomerization of α-olefins with Grubbs 2nd generation catalyst in MeOH, please see: (a) Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481. For a short review

aldehyde **75**, partner for Wittig coupling with the phosphorane derived from bromide **77**. Compound **77** will be prepared in turn from THP tetrad **76**, which comprises the *ABCD* ring system of gambierol and which has been synthesized by Dr. Denise Colby via a water-promoted *endo*-selective cascade of epoxide-opening cyclizations.[57] The product of Wittig olefination, alkene **78**, will then be converted to hemiketal **79** via Ley oxidation[58] and deprotection, setting the stage for alkylative etherification to generate the outstanding *E* ring. We propose converting the hemiketal to a mixed thioketal intermediate, which can then be methylated diastereoselectively to afford **80** either through oxocarbenium formation with mCPBA and subsequent reaction with $AlMe_3$[59] or by direct reaction with Me_2Zn and $Zn(OTf)_2$.[60] Kadota has documented that the latter method is quite mild and that, indeed, a benzylidene acetal is stable under the reaction conditions, suggesting that the 1,3-dioxolane should survive. With the entire ladder polyether core of gambierol thus constructed in **80**, all that would then remain en route to **1** is functional group manipulation and appendage of the triene side chain to the *H* ring.

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of this reaction and other methods to effect the same transformation, see: (b) Donohoe, T. J.; O'Riordan, T. J. C.; Rosa, C. P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1014.

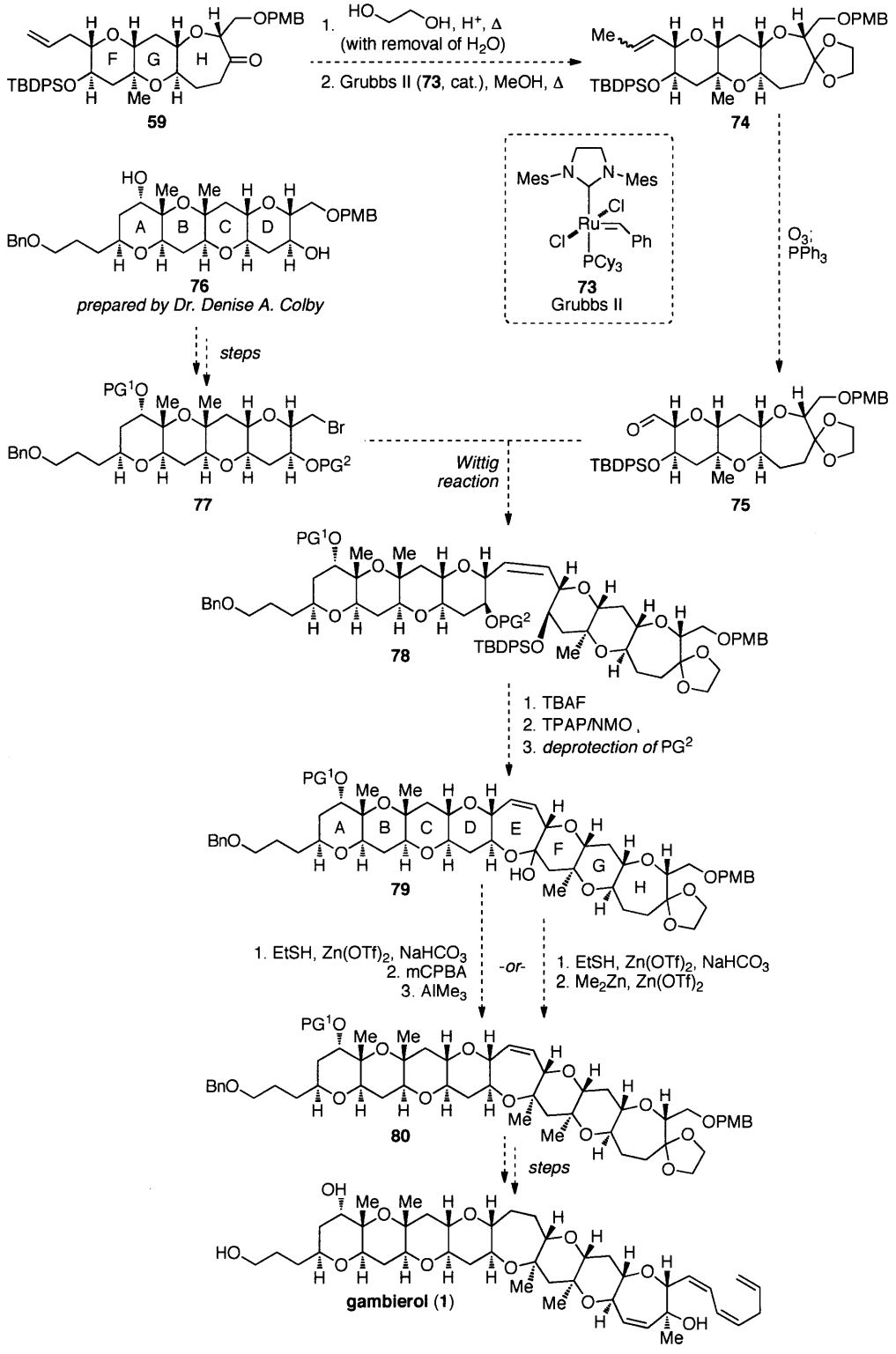
[57] Colby, D. A.; Jamison, T. F. *Unpublished results.*

[58] Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

[59] (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1986**, *108*, 2468. (b) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321.

[60] Kadota, I.; Kishi, T.; Fujisawa, Y.; Yamagami, Y.; Takamura, H. *Tetrahedron Lett.* **2010**, *51*, 3960.

Scheme 17. Plan toward the completion of gambierol.



J. Summary of efforts toward gambierol.

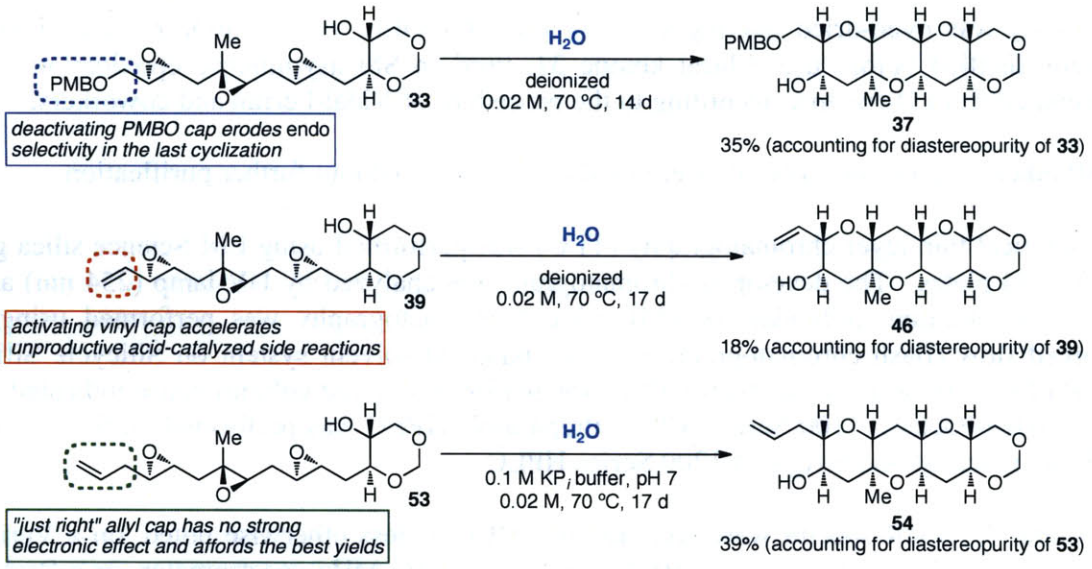
To briefly conclude our work on gambierol, we have successfully assembled its *FGH* ring system in fairly concise fashion. Our approach is built around a water-promoted *endo*-selective cascade of three epoxide-opening cyclizations. Uniquely, this cascade is templated not by a preformed THP ring but rather by a "detachable" 1,3-dioxane ring, which is cleaved after the cascade to reveal synthetic handles for oxepane formation via one-carbon ring expansion. The methylene acetal of the template ring is usefully balanced, as it is robust enough to survive long heating in water but labile enough to be opened under appropriate conditions.

In this work, we cannot claim to be rigorously testing Nakanishi's cascade hypothesis for ladder polyether synthesis, and in truth the transformation of triepoxide **53** to tetracycle **54** (Scheme 18) may stretch the definition of "biomimetic," for a number of reasons. Among them, there is no evidence for methylene acetals or any other kind of 1,3-dioxane ring isolated in secondary metabolites from dinoflagellates that produce these natural products. Additionally, Nature is unlikely to follow our indirect and somewhat inelegant ring expansion route to the oxepane *H* ring. Finally, and perhaps most obviously, the conditions required for the water-promoted reaction of **53** (heating to 70 °C for two weeks) are utterly incongruous with the environment of marine dinoflagellates. Still, we have been inspired throughout by the cascade hypothesis.

Furthermore, this work has reinforced an important lesson relevant to the viability of all *endo*-selective epoxide-opening cascades in water. The behaviors of differently capped triepoxides **33**, **39**, and **53** are all entirely consistent with a stepwise mechanism to their respective *endo* products (Scheme 18). Together, they reiterate the importance of fine-tuning water-promoted cascades. The appendage of alkenyl or methyl substituents to the *endo* site of one or more epoxides in the chain can reinforce *endo* selectivity, as has been documented in many examples. However, these same substituents are likely to encourage acid-promoted side reactions. Conversely, an electron-withdrawing substituent capping the epoxide chain can suppress epoxide protonation and consequent side reactions, but it can accordingly also undermine *endo* selectivity in the desired pathway. An electron-withdrawing substituent can also retard termination of the desired stepwise,

nucleophilic cascade, allowing more time for acid-catalyzed hydrolysis to creep in. Slow initiation of the desired stepwise cascade from the templated alcohol remains an additional problem. Design of a successful water-promoted epoxide-opening cascade requires consideration of all of these factors, but the method remains a powerful one.

Scheme 18. Summary of cascade reactions promoted by neutral water in our approach to the *FGH* rings of gambierol.



K. Experimental Section

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Reactions were magnetically stirred unless otherwise stated. All temperatures are reported in °C.

Dichloromethane, tetrahydrofuran (THF), Et_2O, and triethylamine were purified via an SG Water USA solvent column system. Reactions in water used deionized water without further purification.

Cs_2CO_3 was oven-dried overnight before use. $BF_3 \cdot OEt_2$, AcCl, $Ti(O\textit{i}Pr)_4$ and HMPA were distilled before use. Chiral ketone **31**, used in Shi asymmetric epoxidation was prepared from D-fructose according to the procedure of Vidal-Ferran and coworkers.[61]

All other reagents and solvents were used as obtained, without further purification.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ceric ammonium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). Analytical HPLC was performed on the column phase indicated on a Hewlett-Packard 1100 Series HPLC. Preparative HPLC was performed on the column phase indicated on an Agilent 1200 Series HPLC.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a Varian Inova-500 MHz spectrometer, a Bruker AVANCE-400 MHz spectrometer, or a Bruker AVANCE-600 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual $CHCl_3$ in $CDCl_3$ (7.27 ppm) or C_6HD_5 in C_6H_6 (7.15 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and app = apparent), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm) or C_6D_6 (128.6 ppm), on the δ scale. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR. High Resolution mass spectra (HR-MS) were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Jasco Model 1010 polarimeter at 589 nm.

An X-ray structure of **56** was collected on a Siemens three-circle Platform Diffractometer coupled to a Bruker-APEX CCD detector at the MIT Department of Chemistry X-Ray Diffraction Facility.

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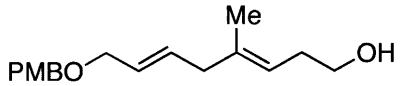
[61] Nieto, N.; Molas, P.; Benet-Buchholz, J.; Vidal-Ferran, A. *J. Org. Chem.* **2005**, *70*, 10143-10146.



26

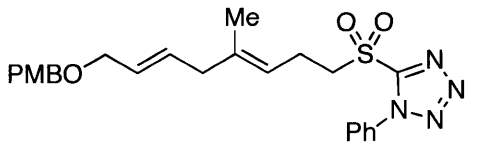
Skipped diene 26: PMB-protected homoallyl alcohol **24**[26] (15.3 g, 79.6 mmol) and 3-pentyn-1-ol **25** (2.23 g, 26.5 mmol) were dissolved in acetone[62] (53 mL), and the resulting solution was sparged vigorously with Ar for 5 min. Solid $CpRu(NCMe)_3PF_6$ (680 mg, 1.57 mmol) was then added in a single portion. The resulting orange-yellow-brown solution was stirred at ambient temperature for 80 min., at which point it was concentrated *in vacuo*. The crude diene **26** was then purified by column chromatography (gradient 30% to 50% to 100% EtOAc in hexanes) to provide diene **26** as a colorless, heavy oil (3.13 g, 10.9 mmol, 41%, as a 10:1 *E*:*Z* mixture at the disubstituted alkene and a 7:1 mixture of branched:linear regioisomers, R_f = 0.47 (50% EtOAc in hexanes)). At this point, these stereo- and regioisomers were not separable by column chromatography, but they could be separated in two steps, after sulfone formation.

IR (thin film, NaCl): 3403, 2933, 2857, 1663, 1613, 1586, 1514, 1464, 1361, 1302, 1248, 1173, 1037 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.69 (dt, *J* = 15.4, 6.8 Hz, 1H), 5.61 (dt, *J* = 15.4, 5.9 Hz, 1H), 5.18 (td, *J* = 7.2, 0.9 Hz, 1H), 4.43 (s, 2H), 3.96 (d, *J* = 5.9 Hz, 2H), 3.79 (s, 3H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.75 (d, *J* = 6.4 Hz, 2H), 2.28 (app q, *J* = 6.8 Hz, 2H), 1.89 (br s, 1H), 1.64 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 136.9, 132.4, 130.5, 129.5, 128.1, 121.2, 113.9, 71.7, 70.5, 62.4, 55.4, 42.7, 31.7, 16.5.

HR-MS (ESI) *m/z* calcd for $C_{17}H_{24}O_3$ $(M+Na)^+$: 299.1618, found 299.1630.



27

Sulfone 27: Primary alcohol **26** (3.00 g, 10.9 mmol), PPh_3 (4.28 g, 16.3 mmol), and 1-phenyltetrazole-5-thiol (3.87 g, 21.7 mmol) were added to a 250 mL round-bottom flask, and then dissolved in THF (109 mL). The resulting solution was cooled to 0 °C. Diisopropyl azodicarboxylate (DIAD, 3.97 g, 3.8 mL, 19.6 mmol) was then added slowly, dropwise, over 5 min., to provide a yellow solution. After stirring 10 min. at 0 °C,

[62] This reaction is not water-sensitive. The acetone does not need to be distilled. In our hands, the reaction worked well in acetone taken directly out of reagent grade bottles.

the reaction was warmed to room temperature and stirred a further 40 min. It was then quenched by pouring into sat. $NaCl_{(aq)}$ (~100 mL). The aqueous layer was extracted with Et_2O (3 x ~200 mL), and the combined organics were washed with sat. $NaCl_{(aq)}$ (~100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide the crude sulfide. The crude product was purified by column chromatography (gradient 6% to 60% EtOAc in hexanes) to provide the sulfide (5.05 g, R_f = 0.60 (30% EtOAc in hexanes)) in approximately 90% purity, which was carried forward into oxidation.

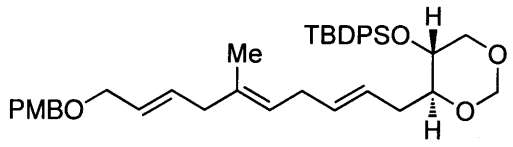
The sulfide product from the previous step was dissolved in EtOH (145 mL), and the resulting solution was cooled to 0 °C. H_2O_2 (a 30% w/w solution in water, 4.94 g of solution, ~43.6 mmol) and $(NH_4)_6Mo_7O_{24}•4H_2O$ (1.35 g, 1.09 mmol) were then added. The reaction was stirred vigorously at 0 °C for 1 h. and then warmed to ambient temperature for 13.5 h. more. Over this time, the mixture's color evolved from white to a bright yellow. The reaction was quenched by pouring into sat. $NaCl_{(aq)}$ (~100 mL). The aqueous layer was extracted with Et_2O (3 x ~200 mL), and the combined organics were washed with sat. $NaCl_{(aq)}$ (2 x ~50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude sulfone **27**. The crude was purified by column chromatography (gradient 15% to 20% to 30% EtOAc in hexanes) to afford **27** (3.20 g, 6.83 mmol, 63% over 2 steps). At this stage the desired isomer (R_f = 0.48 (30% EtOAc in hexanes)) could be separated from the branched regioisomer (R_f = 0.55 (30% EtOAc in hexanes)).

IR (thin film, NaCl): 2922, 2851, 1996, 1610, 1511, 1462, 1339, 1242, 1150 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.65-7.61 (m, 2H), 7.58-7.51 (m, 3H), 7.21 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 5.61-5.51 (m, 2H), 5.09 (tq, J = 7.3, 1.3 Hz, 1H), 4.38 (s, 2H), 3.91 (d, J = 4.7 Hz, 2H), 3.74 (s, 3H), 3.69-3.65 (m, 2H), 2.66 (d, J = 4.8 Hz, 2H), 2.61 (app q, J = 7.7 Hz, 2H), 1.59 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 153.7, 138.8, 133.2, 131.7, 131.4, 130.6, 129.9, 129.6, 128.8, 125.3, 119.2, 114.0, 72.0, 70.5, 55.8, 55.5, 42.5, 21.4, 16.6.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{28}N_4O_4S$ $(M+Na)^+$: 491.1723, found 491.1731.



28

Skipped triene 28: To a solution of sulfone **27** (407 mg, 0.869 mmol) in THF (5.5 mL) cooled to -78 °C was added slowly, over 3 min., a solution of KHMDS (199 mg, 1.00 mmol) in THF (1.2 mL). The resulting yellow-orange solution was stirred for 50 min. at -

78 °C, at which point DMPU (420 μL) was added. A solution of aldehyde **23**[63] (400 mg, 1.04 mmol) was then added slowly, dropwise, over 5 min. The reaction solution was allowed to warm gradually from -78 °C overnight, at which point it was quenched by pouring into sat. $NaCl_{(aq)}$. The aqueous layer was extracted with Et_2O, washed with sat. $NaCl_{(aq)}$, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude triene **28**. The crude was purified by column chromatography (gradient 5% to 40% EtOAc in hexanes) to afford **28** as a colorless oil (465 mg, 0.74 mmol, 85%, as a 10:1 *E*:*Z* mixture at the newly formed alkene, R_f = 0.84 (30% EtOAc in hexanes)).

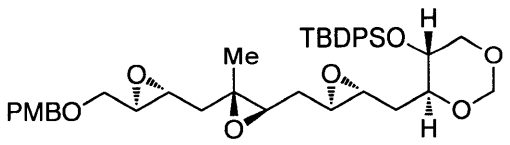
$[\alpha]^{22}_D$ = +3.6 (*c* = 1.22, CH_2Cl_2).

IR (thin film, NaCl): 2932, 2856, 1613, 1588, 1513, 1472, 1428, 1361, 1302, 1248, 1173, 1111, 1038 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.69-7.63 (m, 4H), 7.48-7.43 (m, 2H), 7.43-7.37 (m, 4H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.71 (app dt, *J* = 15.3, 6.6 Hz, 1H), 5.63 (app dt, *J* = 15.3, 6.0 Hz, 1H), 5.47-5.36 (m, 2H), 5.18 (app tq, *J* = 7.2, 1.2 Hz, 1H), 4.90 (d, *J* = 6.0 Hz, 1H), 4.53 (d, *J* = 6.1 Hz, 1H), 4.46 (s, 2H), 3.99 (dd, *J* = 5.9, 0.7 Hz, 1H), 3.84-3.80 (m, 4H), 3.53 (ddd, *J* = 9.7, 9.0, 5.0 Hz, 1H), 3.45 (app td, *J* = 8.5, 2.6 Hz, 1H), 3.31 (app t, *J* = 10.2 Hz, 1H), 2.75 (d, *J* = 6.5 Hz, 2H), 2.70 (app t, *J* = 5.6 Hz, 2H), 2.59 (ddd, *J* = 13.5, 5.3, 2.7 Hz, 1H), 2.09 (ddd, *J* = 13.7, 8.2, 5.8 Hz, 1H), 1.61 (s, 3H), 1.06 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 136.1, 136.0, 134.4, 133.8, 133.1, 132.7, 131.6, 130.7, 130.2, 130.1, 129.6, 128.0, 127.9, 125.8, 123.5, 114.0, 93.4, 82.3, 71.8, 71.6, 70.7, 67.3, 55.5, 42.8, 34.8, 31.6, 27.2, 19.5, 16.3.

HR-MS (ESI) *m/z* calcd for $C_{39}H_{50}O_5Si$ $(M+Na)^+$:649.3320, found 649.3313.



29

Triepoxide 29: To a solution of triene **28** (430 mg, 0.686 mmol) in DMM:MeCN (2:1 v/v, 32.4 mL) was added a 0.05 M aqueous solution of $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} M Na_2EDTA (16.2 mL), nBu_4HSO_4 (58 mg, 0.172 mmol), and chiral ketone **31** (354 mg, 1.37 mmol). The biphasic mixture was stirred vigorously at 0 °C, and Oxone (3.38 g, 5.49 mmol) dissolved in a 4 x 10^{-4} M Na_2EDTA aqueous solution (12.4 mL) was simultaneously added with an aqueous solution of K_2CO_3 (0.89 M, 12.4 mL, 11.0 mmol) over 45 min. via syringe pump. The resulting mixture was stirred an additional 45 min. at

[63] See Chapter IV for the preparation of aldehyde **23**.

0 °C, at which point it was diluted with water (~20 mL). The aqueous layer was separated and extracted three times with Et_2O, and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The incompletely epoxidized mixture was then resubjected to identical conditions twice, for three total rounds of epoxidation. The crude product was then purified by column chromatography using a gradient of solvents (7% to 60% EtOAc in hexanes) to provide the desired triepoxide **29** as a colorless oil (105 mg, 0.160 mmol, 23%, R_f = 0.33 (30% EtOAc in hexanes) and R_f = 0.44 (10% iPrOH in hexanes); enal side product 30 (57 mg, 0.107 mmol, 16%, R_f = 0.33 (30% EtOAc in hexanes) and R_f = 0.38 (10% iPrOH in hexanes); as well as traces of incompletely oxidized mono- and diepoxide intermediates. The overall dr of triepoxide **29** was revealed to be between 2.5:1 and 3.0:1 by HPLC. (Supelco SUPELCOSIL LC-SI 4.6 mm diameter achiral SiO_2 column, 5 μm particle size, 25 cm length; 3.0% *i*PrOH in hexanes, 1 mL/min.; t_R of major diastereomer = 9.1 min.)

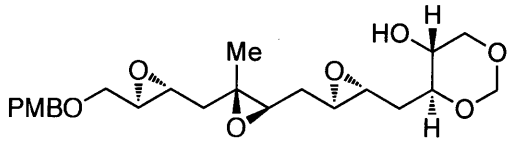
$[\alpha]^{22}_D$ = +12.6 (*c* = 1.40, CH_2Cl_2).

IR (thin film, NaCl): 2959, 2931, 2857, 1612, 1514, 1472, 1428, 1302, 1248, 1174, 1111, 1035 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.69-7.60 (m, 4H), 7.48-7.43 (m, 2H), 7.43-7.37 (m, 4H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.89 (d, *J* = 6.0 Hz, 1H), 4.56-4.51 (m, 2H), 4.48 (d, *J* = 11.5 Hz, 1H), 3.88-3.80 (m, 4H), 3.69 (dd, *J* = 11.4, 3.4 Hz, 1H), 3.58-3.53 (m, 2H), 3.48 (dd, *J* = 11.3, 5.5 Hz, 1H), 3.33 (app t, *J* = 10.0 Hz, 1H), 2.99 (ddd, *J* = 6.9, 4.2, 2.2 Hz, 1H), 2.97-2.93 (m, 2H), 2.85 (ddd, *J* = 6.6, 3.8, 2.3 Hz, 1H), 2.81 (app td, *J* = 5.5, 2.1 Hz, 1H), 1.97 (ddd, *J* = 14.8, 5.9, 1.9 Hz, 1H), 1.90-1.82 (m, 2H), 1.79-1.60 (m, 3H), 1.37 (s, 3H), 1.05 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 136.0, 135.9, 133.6, 132.9, 130.3, 130.2, 130.1, 129.6, 128.1, 127.9, 114.0, 93.3, 80.2, 73.2, 71.6, 70.0, 67.3, 60.4, 59.3, 56.7, 55.8, 55.5, 55.2, 53.0, 41.3, 33.9, 32.0, 27.1, 19.4, 17.2.

HR-MS (ESI) *m/z* calcd for $C_{39}H_{50}O_8Si$ $(M+Na)^+$:697.3167, found 697.3169.



33

Triepoxy alcohol 33: To a solution of TBDPS ether **29** (128 mg, 0.190 mmol) in THF (400 μL) was added TBAF (1 M solution in THF, 380 μL, 0.380 mmol). The reaction solution was stirred 30 min. at ambient temperature and then applied directly to a column of SiO_2 packed in 1:24:75 Et_3N:EtOAc:hexanes. Elution with a gradient of solvent (25%

to 100% EtOAc in hexanes) afford alcohol **33** as a colorless oil (69 mg, 0.159 mmol, 84%, R_f = 0.56 (100% EtOAc)).

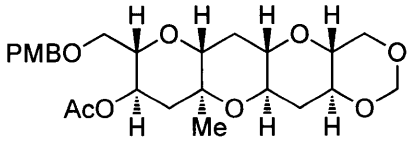
$[\alpha]^{22}_D$ = +12.9 (*c* = 0.64, $CDCl_3$).

IR (thin film, NaCl): 3424, 2921, 2851, 1712, 1612, 1586, 1512, 1462, 1385, 1302, 1243, 1171, 1070, 1023 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.99 (d, *J* = 5.9 Hz, 1H), 4.58 (d, *J* = 6.2 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.13 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.81 (s, 3H), 3.73-3.64 (m, 2H), 3.53-3.44 (m, 2H), 3.32 (app t, *J* = 10.3 Hz, 1H), 3.05 (ddd, *J* = 6.5, 4.8, 2.2 Hz, 1H), 2.99 (ddd, *J* = 7.6, 4.0, 2.2 Hz, 1H), 2.98-2.93 (m, 2H), 2.92 (app td, *J* = 5.7, 2.2 Hz, 1H), 2.69 (br s, 1H), 2.07 (app dt, *J* = 14.8, 4.6 Hz, 1H), 2.00-1.77 (m, 4H), 1.54 (dd, *J* = 14.4, 7.8 Hz, 1H), 1.38 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5, 130.0, 129.7, 114.1, 93.4, 79.7, 73.3, 71.2, 69.8, 65.7, 60.2, 59.4, 57.0, 55.8, 55.7, 55.5, 53.1, 41.3, 34.7, 31.7, 17.2.

HR-MS (ESI) *m/z* calcd for $C_{23}H_{32}O_8$ $(M+Na)^+$: 459.1989, found 459.1982.



34

Acetate 34: A sample of triepoxy alcohol **33** (35.9 mg, 0.082 mmol, in ~3:1 overall dr) was dissolved in pH 7.0 buffer (0.1 M potassium phosphate, 4.1 mL, 0.02 M), and the solution was heated to 70 °C for 20 days. The solution was then cooled to ambient temperature and concentrated *in vacuo* (2 torr, 60 °C) to provide the crude cascade product mixed with potassium phosphate, as a white, semisolid slurry. This crude material was carried into acetylation without further purification.

The crude mixture was suspended in CH_2Cl_2 (2 mL), to which was added Et_3N (34 μL, 24 mg, 0.24 mmol), Ac_2O (11 μL, 12 mg, 0.12 mmol), and DMAP (0.2 mg, 0.001 mmol, added as a solution in CH_2Cl_2). The reaction solution was stirred at ambient temperature for 24 h., then concentrated without extraction. The crude acetylated product was applied directly to a column of SiO_2 and chromatographed with a gradient of solvent (28% to 85% EtOAc in hexanes) to afford the desired tetrad **34** (11.5 mg, 0.024 mmol, 29% over 2 steps, R_f = 0.50 (50% EtOAc in hexanes)), as a white solid, as well as 6,6,6,5-fused

tetracycle **34** (6.8 mg, 0.014 mmol, 17% over 2 steps, R_f = 0.41 (50% EtOAc in hexanes)).

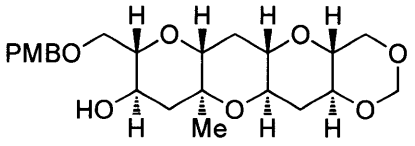
$[\alpha]^{22}_D$ = -19.2 (*c* = 0.38, $CDCl_3$).

IR (thin film, NaCl): 2923, 2848, 1732, 1609, 1512, 1461, 1244, 1168, 1089, 1027 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.02 (d, *J* = 6.2 Hz, 1H), 4.98 (ddd, *J* = 11.1, 10.3, 5.5 Hz, 1H), 4.62 (d, *J* = 6.2 Hz, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.19 (dd, *J* = 10.4, 4.6 Hz, 1H), 3.81 (s, 3H), 3.59-3.41 (m, 5H), 3.33 (ddd, *J* = 11.3, 9.1, 4.1 Hz, 1H), 3.28 (app td, *J* = 9.6, 4.6 Hz, 1H), 3.22 (dd, *J* = 12.2, 3.9 Hz, 1H), 3.16 (ddd, *J* = 11.5, 9.4, 4.4 Hz, 1H), 2.32 (dd, *J* = 11.5, 5.5 Hz, 1H), 2.29 (app dt, *J* = 11.2, 4.0 Hz, 1H), 2.19 (app dt, *J* = 11.6, 4.1 Hz, 1H), 1.93 (s, 3H), 1.67 (app q, *J* = 11.8 Hz, 1H), 1.60 (app q, *J* = 11.2 Hz, 1H), 1.50 (app t, *J* = 11.4, 1H), 1.31 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 159.4, 130.2, 129.7, 113.9, 94.0, 80.3, 79.4, 78.8, 77.5, 74.4, 73.3, 73.2, 69.2, 69.1, 68.8, 67.2, 55.5, 42.8, 35.3, 30.7, 21.2, 15.8.

HR-MS (ESI) *m/z* calcd for $C_{25}H_{34}O_9$ $(M+NH_4)^+$: 496.2541, found 496.2555.



37

Tetracycle 37: ***Note:*** We were unable to cleanly isolate tetrad **37** directly from the cascade reaction of **37**, as it coeluted with **38**, even after attempting separation with a variety of column solvent mixtures (e.g., EtOAc/hexanes, iPrOH/hexanes, $MeOH/CH_2Cl_2$, or $MeOH/CHCl_3$). Thus, to obtain a clean sample of **37**, it was necessary to first isolate acetate **34** and then saponify.

To a solution of acetate **34** (11.5 mg, 0.024 mmol) in THF:MeOH (2:1 v/v, 540 μL) was added an aqueous solution of LiOH (1 M, 60 μL, 0.060 mmol). The reaction solution was stirred at 0 °C for 1 h., then quenched with sat. $NH_4Cl_{(aq)}$ (~1 mL). The primarily aqueous solution was then extracted with Et_2O (5 x ~2 mL). The combined organic solutions were concentrated *in vacuo* without drying, and the crude **37** was purified by column chromatography (50% EtOAc in hexanes) to provide **37** (8.0 mg, 0.018 mmol, 76%, R_f = 0.15 (50% EtOAc in hexanes), 0.66 (100% EtOAc), 0.38 (5% MeOH in $CHCl_3$)) as a transparent film that slowly solidified on standing at -20 °C.

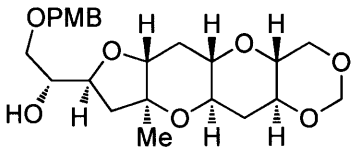
$[\alpha]^{22}_D$ = +19.1 (*c* = 0.38, $CDCl_3$).

IR (thin film, NaCl): 3445, 2923, 2853, 1612, 1514, 1462, 1248, 1166, 1083, 1031 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 5.02 (d, J = 6.2 Hz, 1H), 4.61 (d, J = 6.2 Hz, 1H), 4.53 (d, J = 11.6 Hz, 1H), 4.49 (d, J = 11.6 Hz, 1H), 4.19 (dd, J = 10.3, 4.4 Hz, 1H), 3.86-3.79 (m, 4H), 3.75 (dd, J = 9.6, 4.8 Hz, 1H), 3.60 (dd, J = 9.6, 6.5 Hz, 1H), 3.49-3.38 (m, 3H), 3.36-3.25 (m, 2H), 3.21-3.13 (m, 2H), 2.75 (br s, 1H), 2.29 (app dt, J = 11.2, 3.9 Hz, 1H), 2.23 (dd, J = 11.8, 5.4 Hz, 1H), 2.12 (app dt, J = 11.5, 4.1 Hz, 1H), 1.66-1.56 (m, 2H), 1.52 (app t, J = 11.5 Hz, 1H), 1.24 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 129.7, 114.1, 100.0, 94.0, 80.9, 79.0, 78.8, 77.5, 74.4, 73.7, 73.3, 71.5, 69.2, 69.0, 68.7, 55.5, 45.6, 35.3, 30.7, 29.9, 16.0.

HR-MS (ESI) *m/z* calcd for $C_{23}H_{32}O_8$ $(M+Na)^+$: 459.1989, found 459.1989.



38

***Exo*-tetracycle 38:** R_f = 0.66 (100% EtOAc), 0.43 (5% MeOH in $CHCl_3$).

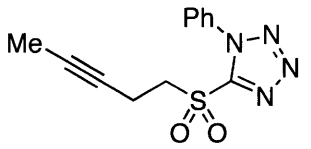
$[\alpha]^{22}_D$ = +9.8 (c = 0.30, CH_2Cl_2).

IR (thin film, NaCl): 3464, 2921, 2854, 1612, 1514, 1463, 1301, 1249, 1166, 1086, 1028 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.02 (d, J = 6.2 Hz, 1H), 4.61 (d, J = 6.2 Hz, 1H), 4.51 (d, J =11.4 Hz, 1H), 4.46 (d, J = 11.4 Hz, 1H), 4.19 (dd, J = 10.3, 4.6 Hz, 1H), 4.07 (app dt, J = 8.8, 6.6 Hz, 1H), 3.96-3.89 (m, 1H), 3.82 (s, 3H), 3.63-3.56 (m, 2H), 3.51 (dd, J = 12.7, 3.4 Hz, 1H), 3.47-3.41 (m, 2H), 3.34 (ddd, J = 11.2, 9.1, 4.2 Hz, 1H), 3.27 (app td, J = 9.5, 4.6 Hz, 1H), 3.19 (ddd, J = 10.8, 9.6, 4.5 Hz, 1H), 2.40 (d, J = 3.1 Hz, 1H), 2.36-2.28 (m, 2H), 2.03 (app t, J = 10.2 Hz, 1H), 1.94 (dd, J = 11.4, 6.8 Hz, 1H), 1.73-1.63 (m, 2H), 1.29 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 130.0, 129.7, 114.1, 94.0, 79.5, 79.3, 78.5, 78.5, 77.5, 74.8, 73.4, 72.7, 71.0, 70.7, 69.2, 55.5, 39.9, 35.6, 29.8, 16.6.

HR-MS (DART) *m/z* calcd for $C_{23}H_{32}O_8$ $(M+NH_4)^+$: 454.2435, found 454.2433.



41

Sulfone 41: Triphenylphosphine (143 g, 547 mmol) and 1-phenyltetrazole-5-thiol (110 g, 618 mmol) were added to a dry round-bottom flask. 3-pentyn-1-ol **25** (40 g, 476 mmol) was added, followed by THF (2.0 L), and the resulting solution was cooled to 0 °C. Diisopropyl azodiacarboxylate (DIAD, 118 g, 113 mL, 585 mmol) was added slowly, dropwise, over 15 min. The resulting orange solution was stirred 10 min. at 0 °C, then allowed to react at ambient temperature for 45 min. It was then quenched with the addition of sat. $NaCl_{(aq)}$ (600 mL), and the biphasic mixture was stirred open to air overnight. The aqueous later was separated and extracted twice with Et_2O (~500 mL each). The combined organics were washed with sat. $NaCl_{(aq)}$ (~200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude sulfide (R_f = 0.57 (30% EtOAc in hexanes)) was carried forward into oxidation without further purification.

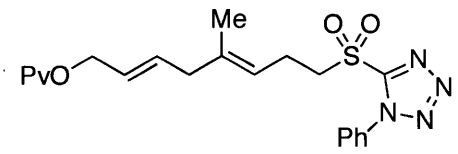
The crude sulfide was dissolved in EtOH (2.3 L) and the resulting solution cooled to 0 °C. H_2O_2 (30% w/w solution in H_2O, 410 g solution, 3.6 mol H_2O_2) was added, followed by $(NH_4)_6Mo_7O_{24}•4H_2O$ (109 g, 88 mmol). The resulting solution was stirred vigorously for 15 min. at 0 °C, then allowed to react at ambient temperature for 43 h. Over this time, the color of the reaction solution gradually evolved from a pale, nearly white yellow to a bright, deep yellow. The reaction was then diluted with sat. $NaCl_{(aq)}$ (2.0 L). The aqueous solution was extracted four times with Et_2O (~600 mL each), and the combined organics were washed with sat. $NaCl_{(aq)}$ (1.0 L), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude sulfone **41** along with multiple byproducts as a chunky, bright yellow solid. This solid was filtered through a pad of SiO_2 using a gradient of solvents (20% to 50% EtOAc in hexanes) to afford a mixture of the sulfone and diisopropyl hydrazodicarboxylate, the reduced byproduct of DIAD. This impurity was removed by recrystallization of the combined solids in an approximately 2:1 mixture of *i*PrOH:H_2O, which provided sulfone **41** as white needles (51 g, 185 mmol, 40% over 2 steps, R_f = 0.54 (30% EtOAc in hexanes)).

IR (thin film, NaCl): 2959, 2921, 1996, 1592, 1499, 1424, 1343, 1332, 1295, 1154, 1131, 1107, 1051 cm^{-1}

^1H NMR (600 MHz, C_6D_6): δ 7.35-7.32 (m, 2H), 7.02-6.96 (m, 3H), 3.29 (t, J = 7.1 Hz, 2H), 2.43 (tq, J = 7.1, 2.5 Hz, 2H), 1.43 (t, J = 2.6 Hz, 3H).

^{13}C NMR (125 MHz, C_6D_6): δ 154.3, 133.9, 131.3, 129.7, 125.8, 79.5, 74.0, 55.1, 14.1, 3.5.

HR-MS (DART) *m/z* calcd for $C_{12}H_{12}N_4O_2S$ $(M+Na)^+$: 277.0754, found 277.0755.



42

Diene 42: Alkene **40**[64] (14.4 g, 92 mmol) and alkyne **41** (12.7 g, 46 mmol) were dissolved in acetone[65] (92 mL), and the resulting solution was sparged with Ar for 5 min. A sample of $CpRu(NCMe)_3PF_6$ (1.20 g, 2.76 mmol) was measured, and 1/3 of this quantity was added to the reaction flask in a single portion. The resulting orange-brown solution was stirred at room temperature for 12 min., at which point another 1/3 portion of catalyst was added. After a further 12 min. had passed, the final portion of catalyst was added. The solution was stirred another 16 min., for a total 40 min. reaction time, and then directly concentrated *in vacuo* to an orange-brown oil. The crude diene **42** was purified by column chromatography (gradient 15% to 20% EtOAc in hexanes) to afford **42** as a yellow-brown oil (16.9 g, 39 mmol, 85%, *E*:*Z* at disubstituted alkene = 6:1, rr (linear:branched) = 6:1) as well as a small amount of unreacted alkyne **41** (1.3 g, 4.7 mmol, 10%). If desired, the branched regioisomer (R_f = 0.58 (30% EtOAc in hexanes)) may be separated away from the desired linear **42** (R_f = 0.52 (30% EtOAc in hexanes)) by diligent column chromatography.

IR (thin film, NaCl): 2973, 2935, 2874, 1725, 1596, 1498, 1481, 1461, 1398, 1346, 1283, 1153, 1033 cm^{-1}.

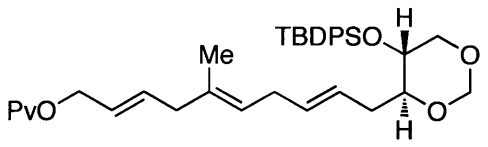
^1H NMR (600 MHz, $CDCl_3$): δ 7.71-7.67 (m, 2H), 7.65-7.58 (m, 3H), 5.68 (dt, J = 15.4, 6.8 Hz, 1H), 5.58 (dt, J = 15.4, 6.0 Hz, 1H), 5.16 (t, J = 6.8 Hz, 1 H), 4.52 (d, J = 5.9 Hz, 2H), 3.73 (m, 2H), 2.72 (d, J = 6.7 Hz, 2H), 2.68 (app q, J = 7.7 Hz, 2H), 1.64 (s, 3H), 1.20 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 178.4, 153.6, 138.4, 133.2, 132.4, 131.6, 129.9, 126.5, 125.2, 119.4, 64.7, 55.8, 42.3, 38.9, 27.4, 21.3, 16.5.

HR-MS (ESI) *m/z* calcd for $C_{21}H_{28}N_4O_4S$ $(M+Na)^+$: 455.1723, found 455.1722.

[64] For the preparation of alkene **40** in one step from homoallyl alcohol, see: Cirakovic, J.; Driver, T. G.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 9370.

[65] It was not found necessary to distill the acetone. Fresh bottles of reagent grade acetone of the type used for washing glassware proved perfectly acceptable for this reaction.



43

Triene 43: To set up the Julia-Kocienski olefination, both aldehyde **23** and sulfone **42** were azeotroped twice with benzene to remove water.
Into a solution of sulfone **42** (28.2, 65 mmol) in THF (400 mL) that had been precooled to -78 °C was slowly, over 5 min., cannulated a solution of KHMDS (16.2 g, 81 mmol) in THF (150 mL). The resulting yellow-orange solution was stirred 1 h. at -78 °C. At this point, DMPU (42 g, 39 mL, 325 mmol) was added. A solution of aldehyde **23** (25.1 g, 65 mmol) in THF (100 mL) was then cannulated in, slowly, over 5 min., while holding the reaction at -78 °C. After stirring 2 h. at -78 °C, the reaction was allowed to warm to room temperature and stirred 15 h. Over this time, the reaction color changed from yellow-orange to an opaque muddy brown. The reaction was quenched by pouring into sat. $NaCl_{(aq)}$ (600 mL) and diluted with Et_2O (300 mL). The aqueous layer was separated and extracted twice with Et_2O (~500 mL each). The combined organics were washed with sat. $NaCl_{(aq)}$ (~200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude triene **43** as a brown oil. The crude product was purified by column chromatography (8% EtOAc in hexanes) to afford **43** as a colorless oil (22.2 g, 37.6 mmol, 58%, ~9:1 *E*:*Z* at newly formed alkene, R_f = 0.62 (15% EtOAc in hexanes)).

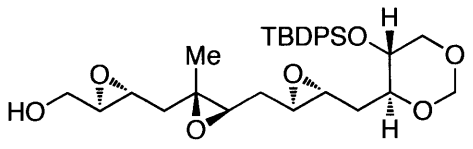
$[\alpha]^{22}_D$ = +3.3 (*c* = 2.3, CH_2Cl_2).

IR (thin film, NaCl): 3072, 2963, 2932, 2858, 2762, 1729, 1590, 1473, 1462, 1428, 1282, 1151, 1111, 1042 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.69-7.62 (m, 4H), 7.48-7.43 (m, 2H), 7.42-7.37 (m, 4H), 5.74 (app dt, *J* = 15.4, 7.0 Hz, 1H), 5.59 (app dt, *J* = 15.3, 6.3 Hz, 1H), 5.43-5.38 (m, 2H), 5.17 (app t, *J* = 7.2 Hz, 1H), 4.90 (d, *J* = 6.0 Hz, 1H), 4.55-4.51 (m, 3H), 3.82 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.53 (app td, *J* = 9.3, 5.0 Hz, 1H), 3.45 (app td, *J* = 8.5, 2.6 Hz, 1H), 3.32 (app t, *J* = 10.3 Hz, 1H), 2.76-2.67 (m, 4H), 2.59 (ddd, *J* = 13.4, 5.4, 2.5 Hz, 1H), 2.09 (ddd, *J* = 13.8, 8.2, 5.3 Hz, 1H), 1.59 (s, 3H), 1.22 (s, 9H), 1.06 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5, 136.1, 136.0, 134.1, 133.8, 133.7, 133.2, 131.5, 130.2, 130.2, 128.0, 127.9, 125.8, 125.7, 123.8, 93.4, 82.4, 71.6, 67.3, 65.0, 42.7, 38.9, 34.8, 31.6, 27.4, 27.2, 19.5, 16.2.

HR-MS (ESI) *m/z* calcd for $C_{36}H_{50}O_5Si$ $(M+Na)^+$: 613.3320, found 613.3322.



44

Triepoxide 44: A solution of pivalate ester **43** (26.5 g, 44.8 mmol) in CH_2Cl_2 (1.07 L) was cooled to -78 °C. A 1 M solution of DIBAL in CH_2Cl_2 (135 mL, 135 mmol) was added slowly, dropwise, over 5 min., and the reaction was stirred at -78 °C for 40 min. The reaction was quenched by slow addition of MeOH (10.3 g, 13.1 mL, 323 mmol) at -78 °C and then allowed to warm to ambient temperature. A saturated aqueous solution of Rochelle's salt (potassium sodium tartrate, 1.0 L) was added, and the biphasic mixture was stirred vigorously overnight. The aqueous layer was then separated and extracted three times with CH_2Cl_2 (~300 mL each). The combined organics were washed with sat. $NaCl_{(aq)}$ (200 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the crude allylic alcohol (R_f = 0.43 (30% EtOAc in hexanes)), which was carried into Sharpless asymmetric epoxidation without further purification.

For Sharpless asymmetric epoxidation, powdered 4 Å molecular sieves (7.2 g) were flame dried and then cooled in a 1 L round bottom flask. To this was added CH_2Cl_2 (200 mL) and $Ti(O\textit{i}Pr)_4$ (1.77 mL, 1.65 g, 5.82 mmol), and the resulting solution was cooled to -20 °C and stirred 10 min. D-(-)-DET (1.30 mL, 1.57 g, 7.61 mmol) was added, and the solution stirred a further 20 min. at -20 °C. A 5-6 M solution of TBHP in decane (17.6 mL, ~97 mmol) was then added dropwise over 3 min., and the resulting solution stirred a further 20 min. at -20 °C. A solution of the crude allylic alcohol product from DIBAL reduction in CH_2Cl_2 (64 mL) was then added dropwise over 10 min. The reaction was stirred at -20 °C for 6 h, then quenched at -20° with 11.2 mL of a 40% NaOH solution in sat. aqueous NaCl (prepared from 10 mL H_2O, 4.5 g NaOH, and 560 mg NaCl). Et_2O (27 mL) was added immediately thereafter, and the mixture was allowed to stir 15 min. at -20°, then warmed to room temperature. $MgSO_4$ (11.2 g) and Celite (1.2 g) were then added, and the resulting suspension was stirred vigorously for 10 min. The suspension was then filtered through a pad of Celite, which was washed with copious quantities of CH_2Cl_2 (~250 mL total). The crude epoxide product solution was concentrated *in vacuo* to a milky, opalescent yellow oil. The crude epoxide (R_f = 0.24 (30% EtOAc in hexanes) was carried forward into Shi epoxidation without further purification.

To a solution of this crude epoxide in CH_3CN (670 mL) was added chiral diacetate ketone **32** (21 g, 70 mmol), Bu_4NHSO_4 (2.3 g, 6.7 mmol), and a 4 x 10^{-4} M aqueous solution of Na_2EDTA (450 mL). The resulting biphasic mixture was cooled to 0 °C and stirred vigorously. $NaHCO_3$ (122 g, 1460 mmol) and Oxone (275 g, 448 mmol) were thoroughly mixed, and this solid mixture was added portionwise over 5 h., in six portions. The aqueous layer was then separated and extracted three times with EtOAc (~400 mL each). The combined organics were washed with sat. $NaCl_{(aq)}$ (~50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude triepoxide **44** as a yellow oil. The crude product was purified by column chromatography (gradient 30% to 50% EtOAc in hexanes) to afford **44** as a colorless oil (14.1 g, 25.4 mmol, 57% over 3 steps, as a 2.0:1 overall mixture of diastereomers, R_f of all diastereomers = 0.32 (70% EtOAc in

hexanes)).
This mixture of diastereomers was carried forward into subsequent reactions. However, a small portion of **44** was purified by preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO2 column, 5μm particle size, 25 cm length; 84:16 hexanes:*i*PrOH, 20 mL/min) to afford a sample of **44** (t_R = 8.2 min.) in ~8:1 dr, which was characterized.

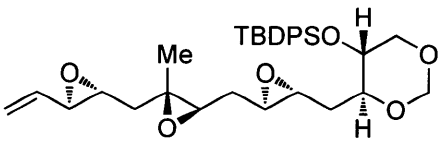
$[\alpha]^{22}_D$ = +12.8 (*c* = 0.36, CH_2Cl_2).

IR (thin film, NaCl): 3448, 3072, 2960, 2930, 2857, 1996, 1590, 1472, 1428, 1390, 1175, 1111, 1034 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.68-7.60 (m, 4H), 7.49-7.43 (m, 2H), 7.43-7.37 (m, 4H), 4.90 (d, *J* = 6.0 Hz, 1H), 4.55 (d, *J* = 6.1 Hz, 1H), 3.90 (ddd, *J* = 12.6, 5.4, 2.9 Hz, 1H), 3.85 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.69 (ddd, *J* = 12.3, 7.6, 4.0 Hz, 1H), 3.60-3.52 (m, 2H), 3.33 (app t, *J* = 10.1 Hz, 1H), 3.12 (ddd, *J* = 7.0, 4.6, 2.2 Hz, 1H), 2.98-2.92 (m, 2H), 2.87-2.80 (m, 2H), 2.00-1.84 (m, 3H), 1.81-1.67 (m, 2H), 1.62 (ddd, *J* = 14.5, 7.2, 5.7 Hz, 1H), 1.37 (s, 3H), 1.05 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.1, 136.0, 133.6, 132.9, 130.4, 130.3, 128.1, 128.0, 93.3, 80.2, 71.6, 67.3, 61.6, 60.3, 59.2, 58.0, 55.8, 55.2, 52.8, 41.1, 33.9, 31.9, 27.2, 19.5, 17.3.

HR-MS (ESI) *m/z* calcd for $C_{31}H_{42}O_7Si$ $(M+Na)^+$: 577.2592, found 577.2605.



45

Vinyl-capped triepoxide 45: A solution of alcohol **44** (57 mg, 0.103 mmol) in CH_2Cl_2 (690 μL) was cooled to 0 °C. To this solution was added DMSO (80 mg, 73 μL, 1.03 mmol), Et_3N (52 mg, 72 μL, 0.51 mmol), and then SO_3•pyridine (65 mg, 0.41 mmol). The reaction solution was stirred 2 min. at 0 °C, then warmed to rt for 80 min. It was then diluted with CH_2Cl_2 (~2 mL), washed three times with sat. $CuSO_4$, and then washed with brine. The organic solution was then dried over $MgSO_4$, filtered, and chromatographic *in vacuo*. The crude aldehyde (R_f = 0.64 (50% EtOAc in hexanes)) was carried into methylenation without further purification.

To a suspension of Ph_3PMeBr (110 mg, 0.309 mmol) in THF (300 μL) cooled to 0 °C was added a solution of KHMDS (58 mg, 0.288 mmol) in THF (400 μL). The resulting bright yellow solution was stirred 1 h. at 0 °C, at which point a solution of the crude aldehyde from the previous step in THF (800 μL) was added slowly, dropwise, over 3

min. The ice bath was then removed, and the orange-red reaction was stirred at ambient temperature for 45 min. The reaction was quenched by pouring into H_2O (~10 mL), and the aqueous layer was extracted three times with Et_2O (~40 mL each). The combined organic layers were washed with brine (~10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude alkene **45**. The crude product was purified by column chromatography (gradient 7% to 60% EtOAc in hexanes) to provide alkene **45** (38 mg, 0.069 mmol, 67% over 2 steps, R_f = 0.50 (30% EtOAc in hexanes)).
A small portion of **45** was later purified by preparative HPLC (Supelco SUPELCOSIL LC-SI, 20 mm diameter achiral SiO2 column, 5μm particle size, 25 cm length; 1.1% iPrOH in hexanes, 20 mL/min) to afford a sample of **45** (t_R = 7.1 min.) in ~7:1 dr, which was characterized.

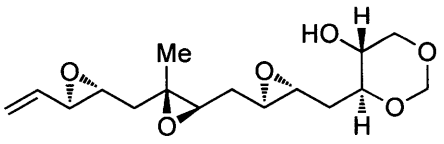
$[\alpha]^{22}_D$ = +4.3 (*c* = 0.15, CH_2Cl_2).

IR (thin film, NaCl): 2957, 2922, 2852, 1734, 1463, 1174, 1110 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.68-7.61 (m, 4H), 7.49-7.43 (m, 2H), 7.43-7.37 (m, 4H), 5.59 (ddd, *J* = 17.3, 10.0, 7.3 Hz, 1H), 5.50 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.30 (dd, *J* = 10.1, 1.5 Hz, 1H), 4.89 (d, *J* = 6.0 Hz, 1H), 4.55 (d, *J* = 6.1 Hz, 1H), 3.85 (dd, *J* = 11.0, 4.4 Hz, 1H), 3.60-3.52 (m, 2H), 3.33 (app t, *J* = 10.0 Hz, 1H), 3.12 (dd, *J* = 7.4, 2.0 Hz, 1H), 3.00 (ddd, *J* = 6.9, 4.5, 2.1 Hz, 1H), 2.95 (dd, *J* = 7.0, 5.5 Hz, 1H), 2.87-2.80 (m, 2H), 1.97 (ddd, *J* = 14.4, 6.0, 2.4 Hz, 1H), 1.92-1.84 (m, 2H), 1.81-1.61 (m, 3H), 1.37 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.1, 136.0, 135.4, 133.7, 132.9, 130.4, 130.2, 128.1, 128.0, 119.9, 93.3, 80.2, 71.6, 67.3, 60.4, 59.3, 58.5, 57.2, 55.8, 55.2, 41.5, 33.9, 32.0, 27.2, 19.5, 17.3.

HR-MS (DART) *m/z* calcd for $C_{32}H_{42}O_6Si$ $(M+H)^+$: 551.2823, found 551.2839.

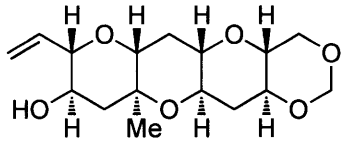


39

Triepoxy alcohol 39: To a solution of TBDPS ether **45** (23.8 mg, 0.043 mmol) in THF (400 μL) cooled to 0 °C was added TBAF (1 M solution in THF, 86 μL, 0.086 mmol). The reaction solution was stirred 45 min. at 0 °C, then applied directly to a column of SiO_2 that had been packed in 2:28:70 Et_3N:EtOAc:hexanes. The column was run with a gradient of solvents (30% to 100% EtOAc in hexanes) to provide triepoxy alcohol **39** (12.8 mg, 0.041 mmol, 95%, R_f = 0.48 (100% EtOAc)).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.58 (ddd, J = 17.2, 9.8, 7.3 Hz, 1H), 5.50 (dd, J = 17.2, 1.8 Hz, 1H), 5.32 (dd, J = 10.0, 1.8 Hz, 1H), 5.01 (d, J = 6.0 Hz, 1H), 4.59 (d, J = 6.2 Hz, 1H), 4.17 (dd, J = 10.7, 5.0 Hz, 1H), 3.71 (app septet, J = 4.9 Hz, 1H), 3.50 (ddd, J = 9.6, 5.6, 4.5 Hz, 1H), 3.33 (app t, J = 10.4 Hz, 1H), 3.13 (dd, J = 7.3, 2.0 Hz, 1H), 3.05 (ddd, J = 6.7, 4.6, 2.3 Hz, 1H), 3.00 (ddd, J = 7.6, 4.1, 2.2 Hz, 1H), 2.99-2.93 (m, 2H), 2.54 (br d, J = 5.8 Hz, 1H), 2.10 (app dt, J = 14.9, 4.4 Hz, 1H), 2.02-1.90 (m, 2H), 1.87-1.78 (m, 2H), 1.60 (dd, J = 14.3, 7.6 Hz, 1H), 1.39 (s, 3H).

HR-MS (DART) *m/z* calcd for $C_{16}H_{24}O_6$ $(M+H)^+$: 313.1646, found 313.1646.



46

Vinyl-capped tetrad 46: A sample of triepoxide **39** (3.1 mg, 0.010 mmol, in 4:1 overall dr) was dissolved in deionized water (500 μL, 0.02 M). The solution was heated to 70 °C for 16 days. Triepoxide **39** appeared to be slightly insoluble in water at room temperature, but the solution cleared on heating. The reaction solution was concentrated *in vacuo* (2 torr, 40 °C). The crude cascade products were purified by column chromatography (50% EtOAc in hexanes) to provide **46** (0.5 mg, 0.0016 mmol, 16%, R_f = 0.38 (100% EtOAc)).

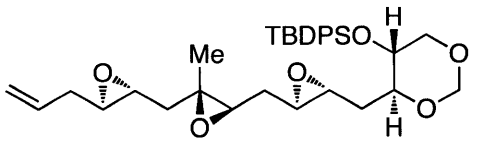
$[\alpha]^{22}_D$ = +31.0 (c = 0.34, CH_2Cl_2).

IR (thin film, NaCl): 3514, 2985, 2960, 2920, 2879, 2853, 2783, 1737, 1457, 1388, 1355, 1315, 1266, 1214, 1166, 1101, 1083, 1075, 1039, 1024 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (ddd, J = 17.3, 10.5, 6.8 Hz, 1H), 5.45 (d, J = 17.1 Hz, 1H), 5.37 (d, J = 10.5 Hz, 1H), 5.02 (d, J = 6.2 Hz, 1H), 4.62 (d, J = 6.2 Hz, 1H), 4.19 (dd, J = 10.4, 4.4 Hz, 1H), 3.65-3.55 (m, 2H), 3.48 (ddd, J = 11.3, 9.5, 4.0 Hz, 1H), 3.43 (app t, J = 10.1 Hz, 1H), 3.34 (ddd, J = 11.1, 9.0, 4.1 Hz, 1H), 3.29 (app td, J = 9.4, 4.6 Hz, 1H), 3.24 (dd, J = 12.3, 3.8 Hz, 1H), 3.19 (ddd, J = 11.5, 9.5, 4.5 Hz, 1H), 2.30 (app dt, J = 11.1, 3.9 Hz, 1H), 2.27 (dd, J = 11.5, 4.3 Hz, 1H), 2.16 (app dt, J = 11.5, 4.1 Hz, 1H), 1.76-1.58 (m, 3H), 1.56 (app t, J = 11.0 Hz, 1H), 1.28 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.6, 120.0, 94.0, 85.6, 79.0, 78.8, 77.5, 74.4, 73.6, 69.2, 69.0, 68.9, 45.6, 35.3, 30.7, 16.0.

HR-MS (DART) *m/z* calcd for $C_{16}H_{24}O_6$ $(M+H)^+$: 313.1646, found 313.1650.



52

Allyl-capped triepoxide 52: PPh_3 (9.2 g, 35 mmol) and imidazole (3.8 g, 56 mmol) were dissolved in Et_2O/MeCN (1:1 v/v, 64 mL), and the resulting solution was cooled to 0 °C. Solid I_2 (9.9 g, 39 mmol) was then added in 8 small portions over 5 minutes, to provide an orange-red solution with large quantities of yellow precipitate. This mixture was warmed to room temperature for 5 min., then recooled to 0 °C. A solution of alcohol **44** (16.0 g, 28 mmol) in Et_2O (60 mL) was then added, slowly, dropwise over 10 min. At this point the cooling bath was removed, and the reaction was stirred at ambient temperature for 25 min. The reaction was then quenched by pouring into sat. $NHCO_{3(aq)}$ (~100 mL) and diluted with Et_2O (~150 mL). The aqueous layer was separated and extracted with Et_2O (3 x ~250 mL). The combined organics were washed with sat. $Na_2S_2O_{3(aq)}$ (~50 mL), until the red color was destroyed. The combined organics were then washed with sat. $NHCO_{3(aq)}$ (~50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide the crude iodide as a pale yellow oil. The crude was purified by column chromatography (packed SiO_2 in 2:28:70 Et_3N:EtOAc:hexanes; eluted with 30% EtOAc in hexanes) to provide the iodide as a colorless oil (17.4 g, 0.026 mmol, 93%, R_f = 0.60 (30% EtOAc in hexanes)). The product was stored frozen in benzene until needed.

The primary alkyl iodide formed in the previous step was dissolved in THF (22 mL). Meanwhile, to a sample of CuI (606 mg, 3.2 mmol) was added recently distilled HMPA (15 mL, 15.2 g, 85 mmol) and THF (20 mL). The pale yellow suspension was stirred at room temperature for 15 min. The primary alkyl iodide solution was then added at room temperature, to provide a brown-yellow solution. After cooling the solution to -25 °C, a solution of vinylmagnesium bromide[66] (1.0 M in THF, 42 mL, 42 mmol) was slowly added, dropwise, over 5 min. Upon addition of the first drops of vinyl Grignard, the reaction solution turned dark gray. As more Grignard was added, the solution became paler gray-yellow. The reaction was stirred 20 min. at -25 °C, then quenched at low temperature with sat. $NH_4Cl_{(aq)}$ (150 mL). After warming to ambient temperature, the biphasic mixture was poured into Et_2O (~150 mL). After extraction, the aqueous layer was separated and extracted again with Et_2O (3x ~250 mL). The combined organics were washed with sat. $NaCl_{(aq)}$ (~75 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to furnish crude alkene **52** as a yellow oil. The crude product was purified by column chromatography (gradient 7% to 60% EtOAc in hexanes) to provide **52** as a colorless oil (10.5 g, 18.6 mmol, 88%, R_f = 0.54 (30% EtOAc in hexanes)).

$[\alpha]^{22}_D$ = +20.6 (*c* = 1.23, $CDCl_3$).

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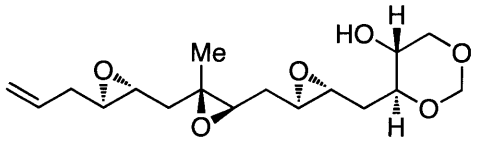
[66] We have found that when using a commercial solution of vinylmagnesium bromide, it is absolutely essential to use a solution that is clear. Clear orange solutions have always worked well; use of cloudy brown or red solutions led to low yields.

IR (thin film, NaCl): 3072, 2962, 2930, 2857, 1642, 1589, 1472, 1428, 1389, 1362, 1293, 1254, 1228, 1175, 1111, 1035 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 7.68-7.61 (m, 4H), 7.48-7.43 (m, 2H), 7.43-7.37 (m, 4H), 5.84 (dddd, J = 17.1, 10.3, 6.7, 6.7 Hz, 1H), 5.17 (dd, J = 17.2, 1.6 Hz, 1H), 5.12 (dd, J = 10.2, 1.5 Hz, 1H), 4.89 (d, J = 6.0 Hz, 1H), 4.55 (d, J = 6.1 Hz, 1H), 3.85 (dd, J = 10.7, 3.9 Hz, 1H), 3.59-3.52 (m, 2H), 3.33 (app t, J = 10.0 Hz, 1H), 2.95 (dd, J = 7.1, 5.3 Hz, 1H), 2.89 (ddd, J = 6.9, 4.5, 2.2 Hz, 1H), 2.87-2.80 (m, 2H), 2.78 (app td, J = 5.5, 2.1 Hz, 1H), 2.39-2.28 (m, 2H), 1.97 (ddd, J = 14.5, 5.9, 2.1 Hz, 1H), 1.87 (ddd, J = 14.5, 7.2, 4.1 Hz, 1H), 1.82 (dd, J = 14.3, 4.5 Hz, 1H), 1.80-1.72 (m, 1H), 1.71-1.61 (m, 2H), 1.37 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.0, 135.9, 133.6, 133.1, 132.9, 130.3, 130.2, 128.1, 127.9, 117.9, 93.3, 80.2, 71.6, 67.3, 60.4, 59.4, 57.3, 55.8, 55.2, 55.0, 41.5, 36.3, 33.9, 32.0, 27.1, 19.4, 17.2.

HR-MS (ESI) *m/z* calcd for $C_{33}H_{44}O_6Si$ $(M+Na)^+$: 587.2799, found 587.2776.



53

Triepoxy alcohol 53: To a solution of silyl ether **52** (9.4 g, 16.6 mmol) in THF (20 mL) was added a solution of TBAF (1 M in THF, 31 mL, 31 mmol). The reaction was stirred at ambient temperature for 1.5 h., at which point it was applied directly to a column of SiO_2 (packed with 1:24:75 Et_3N:EtOAc:hexanes, eluted with a gradient (25% to 50% to 100 EtOAc in hexanes). Pure triepoxy alcohol **53** was obtained as a colorless oil that partially solidified on standing at -20 °C (5.3 g, 14.7 mmol, 88%, R_f = 0.59 (100% EtOAc)).

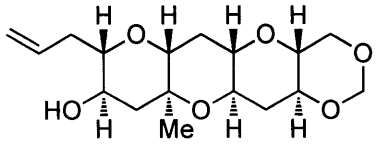
$[\alpha]^{22}_D$ = +20.0 (c = 0.65, CH_2Cl_2).

IR (thin film, NaCl): 3439, 3078, 2978, 2922, 2853, 2773, 1996, 1642, 1462, 1432, 1387, 1253, 1174, 1137, 1073, 1027 cm^{-1}.

^1H NMR (600 MHz, C_6D_6): δ 5.70 (dddd, J = 17.1, 10.2, 6.7, 6.7 Hz, 1H), 5.03 (dd, J = 17.2, 1.4 Hz, 1H), 5.00 (app d, J = 10.3 Hz, 1H), 4.27 (d, J = 6.0 Hz, 1H), 4.03 (dd, J = 10.6, 5.1 Hz, 1H), 3.60-3.54 (m, 1H), 3.28 (app dt, J = 9.1, 5.0 Hz, 1H), 3.15 (app t, J = 10.4 Hz, 1H), 2.96 (app td, J = 5.5, 2.0 Hz, 1H), 2.81 (app t, J = 6.4 Hz, 1H), 2.70 (ddd, J = 6.5, 5.0, 1.8 Hz, 1H), 2.64 (ddd, J = 6.7, 3.9, 2.0 Hz, 1H), 2.43 (app td, J = 5.4, 1.9 Hz, 1H), 2.18 (br s, 1H), 2.09-1.98 (m, 2H), 1.91-1.86 (m, 2H), 1.64-1.56 (m, 2H), 1.45 (app dt, J = 13.3, 6.4 Hz, 1H), 1.31 (dd, J = 14.1, 7.6 Hz, 1H), 1.16 (s, 3H).

^{13}C NMR (100 MHz, C_6D_6): δ 133.9, 117.8, 93.6, 80.2, 71.7, 66.1, 60.3, 59.2, 57.3, 56.0, 55.7, 55.1, 42.0, 36.7, 35.3, 32.3, 17.4.

HR-MS (DART) *m/z* calcd for $C_{17}H_{26}O_6$ $(M+H)^+$: 327.1802, found 327.1799.



54

Tetracycle 54: A sample of triepoxy alcohol **53** (2.03 g, 6.2 mmol, in 2.0:1 overall dr) was dissolved in pH 6.5 buffer (0.1 M potassium phosphate, 248 mL, 0.025 M), and the resulting slightly cloudy suspension was heated to 70 °C for 15 d. On heating, the cloudy solution became completely clear. After several days of heating, the solution became slightly yellow in color. The reaction solution was cooled to room temperature and extracted with EtOAc (5 x ~300 mL). The combined organics were concentrated *in vacuo* without drying. The crude cascade product was then chromatographed (2.5% MeOH in CH_2Cl_2) to provide the desired tetracycle **54** (560 mg, 1.72 mmol, 27%, R_f = 0.64 (10% MeOH in CH_2Cl_2) as well as 6,6,6,5-fused tetracycle **55** (~100 mg, ~0.31 mmol, ~5%, R_f = 0.69 (10% MeOH in CH_2Cl_2)). Desired tetracycle **54** was collected as a colorless oil, but it solidified to a white solid on standing at -20 °C.

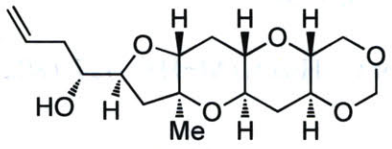
$[\alpha]^{22}_D$ = +13.9 (*c* = 0.58, CH_2Cl_2).

IR (thin film, NaCl): 3458, 3075, 2935, 2858, 2775, 1641, 1460, 1386, 1285, 1166, 1098, 1081, 1029, 1014 cm^{-1}.

^{1}H (600 MHz, $CDCl_3$): δ 5.94 (dddd, *J* = 17.2, 10.2, 7.0, 7.0, 1H), 5.17 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.11 (d, *J* = 10.2, 1H), 5.02 (d, *J* = 6.2 Hz, 1H), 4.62 (d, *J* = 6.2 Hz, 1H), 4.19 (dd, *J* = 10.4, 4.6 Hz, 1H), 3.64 (app td, *J* = 10.1, 5.2 Hz, 1H), 3.49-3.41 (m, 2H), 3.34 (ddd, *J* = 11.1, 9.1, 4.1 Hz, 1H), 3.28 (app td, *J* = 9.5, 4.6 Hz, 1H), 3.24 (ddd, *J* = 9.5, 6.7, 4.4 Hz, 1H), 3.20-3.14 (m, 2H), 2.56 (app dt, *J* = 14.7, 5.7 Hz, 1H), 2.36 (app dt, *J* = 14.7, 6.8 Hz, 1H), 2.29 (app dt, *J* = 11.2, 4.0 Hz, 1H), 2.22 (dd, *J* = 11.6, 5.3 Hz, 1H), 2.12 (app dt, *J* = 11.5, 4.1 Hz, 1H), 1.66-1.54 (m, 3H), 1.50 (app t, *J* = 11.4 Hz, 1H), 1.24 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 134.8, 117.6, 94.0, 83.1, 79.1, 78.9, 77.5, 74.4, 73.6, 69.2, 69.2, 69.0, 46.6, 36.9, 35.3, 30.7, 16.0.

HR-MS (ESI) *m/z* calcd for $C_{17}H_{26}O_6$ $(M+Na)^+$: 327.1802, found 327.1809.



54

***Exo* tetracycle 54:** $R_f = 0.69$ (10% MeOH in CH_2Cl_2).

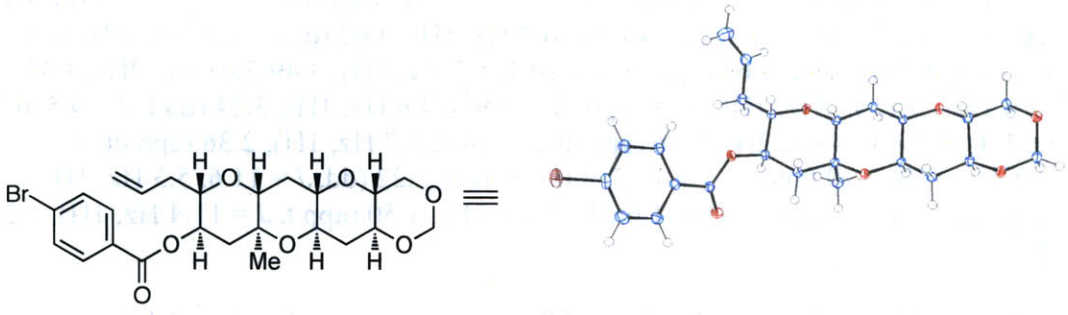
$[\alpha]^{22}_D = +26.8$ ($c = 0.12$, CH_2Cl_2).

IR (thin film, NaCl): 3477, 2919, 2855, 1457, 1374, 1322, 1166, 1087, 1025 cm^{-1}.

^1H (600 MHz, $CDCl_3$): δ 5.83 (dddd, J = 17.2, 10.1, 7.1, 7.1 Hz, 1H), 5.21-5.13 (m, 2H), 5.03 (d, J = 6.1 Hz, 1H), 4.63 (d, J = 6.1 Hz, 1H), 4.18 (dd, J = 10.3, 4.6 Hz, 1H), 4.10 (ddd, J = 8.7, 7.1, 4.6 Hz, 1H), 3.84-3.78 (m, 2H), 3.45-3.38 (m, 2H), 3.38-3.27 (m, 2H), 3.17 (ddd, J = 10.8, 9.6, 5.1 Hz, 1H), 2.34 (app dt, J = 11.2, 4.2 Hz, 1H), 2.31-2.25 (m, 1H), 2.24-2.15 (m, 3H), 1.93 (br s, 1H), 1.85 (dd, J = 13.3, 6.9 Hz, 1H), 1.62 (app q, J = 11.0 Hz, 2H), 1.41 (s, 3H).

^{13}C (125 MHz, $CDCl_3$): δ 134.3, 118.5, 94.0, 81.1, 79.5, 79.0, 77.2, 75.3, 73.9, 71.8, 70.0, 69.2, 38.0, 35.3, 33.9, 31.2, 28.4.

HR-MS (ESI) *m/z* calcd for $C_{17}H_{26}O_6$ $(M+Na)^+$: 327.1802, found 327.1798.



56

***p*-Bromobenzoate 56:** To a solution of alcohol **54** (31 mg, 0.096 mmol) in CH_2Cl_2 (480 μL) was added pyridine (23 mg, 23 μL, 0.29 mmol) and *p*-bromobenzoyl chloride (32 mg, 0.14 mmol). The resulting solution was stirred at room temperature for 14 h., at which point it was concentrated without extraction, to a solid white film. This was

chromatographed (gradient 7% to 60% EtOAc in hexanes) to provide *p*-bromobenzoate **56** as a white solid (28 mg, 0.055 mmol, 57%, R_f = 0.60 (30% EtOAc in hexanes)).

A crystal of **56** suitable for X-ray diffraction was grown by dissolving **56** (~20 mg) in $CDCl_3$ in an NMR tube and then layering hexanes on top. Slow diffusion of hexanes into $CDCl_3$ induced crystallization. Details of the X-ray structure of **56** are provided at the end of this Experimental Section. The sample is saved on MIT's Reciprocal Net server as sample #11014.

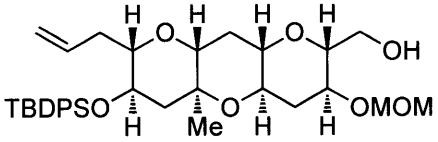
$[\alpha]^{22}_D$ = -1.0 (*c* = 1.22, CH_2Cl_2).

IR (thin film, NaCl): 2950, 2873, 2848, 1742, 1590, 1474, 1394, 1271, 1170, 1121, 1088, 1032, 1011 cm^{-1}.

^1H (600 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 5.91-5.82 (m, 1H), 5.08-5.00 (m, 4H), 4.62 (d, *J* = 6.2 Hz, 1H), 4.19 (dd, *J* = 10.4, 4.5 Hz, 1H), 3.60 (ddd, *J* = 10.2, 7.0, 3.9 Hz, 1H), 3.48 (ddd, *J* = 11.2, 10.0, 4.0 Hz, 1H), 3.44 (app t, *J* = 10.2 Hz, 1H), 3.34 (ddd, *J* = 11.5, 9.2, 4.0 Hz, 1H), 3.18 (ddd, *J* = 11.5, 9.8, 4.4 Hz, 1H), 2.45-2.37 (m, 2H), 2.32-2.25 (m, 2H), 2.16 (app dt, *J* = 11.5, 4.0 Hz, 1H), 1.69-1.57 (m, 3H), 1.34 (s, 3H).

^{13}C (150 MHz, $CDCl_3$): δ 164.9, 133.7, 132.0, 131.3, 128.9, 128.6, 117.8, 94.0, 80.4, 79.4, 78.8, 74.4, 73.4, 71.0, 69.2, 69.1, 43.1, 36.6, 35.3, 30.7, 15.9.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{29}BrO_7$ $(M+Na)^+$: 509.1169, found 509.1158.



57

Methoxymethyl ether 57: To a solution of alcohol **54** (280 mg, 0.76 mmol) in DMF (760 μL) was added imidazole (260 mg, 3.8 mmol) and TBDPSCl (520 mg, 1.9 mmol). The resulting solution was heated to 60 °C for 4 h., at which point it was cooled to room temperature and quenched by pouring into sat. $NH_4Cl_{(aq)}$ (~10 mL). The aqueous layer was extracted with Et_2O (3 x ~40 mL), and the combined organics were washed with sat. $NaCl_{(aq)}$ (~10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude silyl ether was purifed by column chromatography (gradient 5% to 40% EtOAc in hexanes) to provide the product as a white solid (390 mg, 0.69 mmol, 90%, R_f = 0.50 (20% EtOAc in hexanes)).

To a solution of this methylene acetal (100 mg, 0.18 mmol) in Et_2O (180 μL) was added $ZnCl_2$ (12.5 mg, 0.090 mmol) and freshly distilled acetyl chloride (63 μL, 69 mg, 0.89

mmol). The reaction mixture was stirred at room temperature for 35 min., during which time it gradually became dark brown. It was quenched at 0 °C with a solution of NaOMe in MeOH (25% (w%), 2.3 g of solution (~570 mg NaOMe), 2.9 mL, ~10.6 mmol NaOMe) that had been precooled to 0 °C. The quench solution was stirred at 0 °C for 5 min., then warmed to ambient temperature and stirred a further 10 min. Excess NaOMe was neutralized by pouring the solution into sat. $NH_4Cl_{(aq)}$ (~5 mL). The aqueous solution was extracted with Et_2O (4 x ~20 mL), and the combined organics were washed with brine (~10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide crude MOM ether **57** as a yellow oil. The crude product was purified by chromatography (gradient 7% to 100% EtOAc in hexanes) to provide **57** (75 mg, 0.127 mmol, 72%, R_f = 0.23 (30% EtOAc in hexanes)) as a pale yellow oil, as well as some of the methylene acetal starting material (20 mg, 0.035 mmol, 20%, R_f = 0.65 (30% EtOAc in hexanes)).

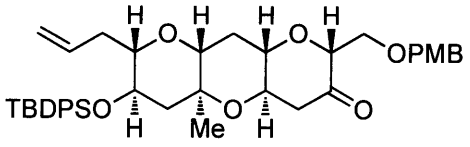
$[\alpha]^{22}_D$ = -12.5 (*c* = 1.19, CH_2Cl_2).

IR (thin film, NaCl): 3481, 3072, 2933, 2890, 2858, 1641, 1590, 1472, 1428, 1380, 1277, 1144, 1103, 1038 cm^{-1}.

^1H (500 MHz, $CDCl_3$): δ 7.70-7.65 (m, 4H), 7.47-7.41 (m, 2H), 7.41-7.36 (m, 4H), 5.83 (dddd, *J* = 17.1, 10.7, 6.8, 6.8 Hz, 1H), 5.03-4.96 (m, 2H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 3.84 (ddd, *J* = 11.4, 5.7, 2.4 Hz, 1H), 3.68 (app dt, *J* = 11.5, 5.6 Hz, 1H), 3.60 (ddd, *J* = 10.8, 9.7, 4.8 Hz, 1H), 3.50 (ddd, *J* = 10.8, 9.3, 5.0 Hz, 1H), 3.40-3.33 (m, 4H), 3.27 (ddd, *J* = 9.4, 4.9, 2.7 Hz, 1H), 3.22 (ddd, *J* = 11.5, 9.4, 3.9 Hz, 1H), 3.13 (dd, *J* = 12.3, 3.8 Hz, 1H), 3.06 (ddd, *J* = 11.3, 9.4, 4.5 Hz, 1H), 2.65-2.58 (m, 1H), 2.36 (app dt, *J* = 11.3, 4.3 Hz, 1H), 2.13-2.03 (m, 3H), 1.88 (dd, *J* = 11.6, 5.0 Hz, 1H), 1.58-1.40 (m, 3H), 1.05 (s, 9H), 0.83 (s, 3H).

^{13}C (100 MHz, $CDCl_3$): δ 136.2, 136.1, 135.0, 133.9, 133.4, 130.1, 129.9, 127.8, 127.8, 116.9, 95.7, 83.5, 80.9, 78.9, 78.1, 73.4, 71.5, 70.6, 68.4, 62.5, 55.9, 46.9, 36.4, 36.1, 30.8, 27.2, 19.5, 15.5.

HR-MS (ESI) *m/z* calcd for $C_{34}H_{48}O_7Si$ $(M+Na)^+$: 619.3062, found 619.3073.



58

Ketone 58: To a solution of alcohol **57** (119 mg, 0.199 mmol) in CH_2Cl_2 (1.17 mL) was added *p*-methoxybenzyl-2,2,2-trichloroacetimidate (85 mg, 62 μL, 0.30 mmol) and (+)-CSA (7.0 mg, 0.030 mmol). The yellow reaction solution was stirred at room temperature for 3.5 h., then quenched by addition of sat. $NHCO_{3(aq)}$ (~2 mL). The mixture was diluted with CH_2Cl_2 (~10 mL) and water (~5 mL) and extracted. The aqueous layer was

separated and extracted with CH_2Cl_2 (4 x ~10 mL). The combined organics were washed with brine (~5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography (gradient 7% to 60% EtOAc in hexanes) to provide the PMB ether (R_f = 0.58 (30% EtOAc in hexanes)), which was contaminated with considerable quantities of PMB-containing side products. This mixture was carried forward into MOM ether deprotection.

The impure PMB ether from the preceding step was dissolved in tBuOH (1.3 mL) in a microwave vial. To this solution was added pyridinium *p*-toluenesulfonate (250 mg, 0.99 mmol). The vial was sealed and heated to 100 °C by microwave irradiation for 2 h. After cooling to ambient temperature, the reaction solution was diluted with Et_2O (5 mL) and quenched with sat. $NaHCO_{3(aq)}$ (~4 mL). After extraction, the aqueous layer was extracted further with Et_2O (4 x ~10 mL). The combined organics were washed with brine (~10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (gradient 7% to 60% EtOAc in hexanes) to afford the free 2° alcohol (56 mg, 0.084 mmol, 42% over 2 steps, R_f = 0.34 (30% EtOAc in hexanes)).

The alcohol from the preceding step (56 mg, 0.084 mmol) was dissolved in CH_2Cl_2 (830 μL). To this was added solid $NaHCO_3$ (7.0 mg, 0.083 mmol) and Dess-Martin periodinane (71 mg, 0.166 mmol). The reaction mixture was stirred at ambient temperature for 14 h., then diluted by addition of CH_2Cl_2 (~3 mL) and quenched by addition of sat. $NaHCO_{3(aq)}$ (~1 mL) and sat. $Na_2S_2O_{3(aq)}$ (~1 mL). After extracted, the aqueous layer was extracted further with Et_2O (4 x ~3 mL). The combined organics were washed with brine (~1 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (gradient 7% to 60% EtOAc in hexanes) to provide ketone **58** (37 mg, 0.055 mmol, 66%, R_f = 0.59 (30% EtOAc in hexanes)).

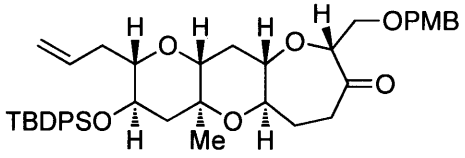
$[\alpha]^{22}_D$ = -48.8 (*c* = 0.42, CH_2Cl_2).

IR (thin film, NaCl): 3072, 2931, 2857, 1726, 1612, 1588, 1514, 1463, 1428, 1363, 1302, 1248, 1173, 1112, 1079 cm^{-1}.

^1H (500 MHz, $CDCl_3$): δ 7.71-7.65 (m, 4H), 7.47-7.36 (m, 6H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.83 (dddd, *J* = 17.2, 10.6, 6.8, 6.8 Hz, 1H), 5.04-4.97 (m, 2H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.8 Hz, 1H), 3.98 (dd, *J* = 5.8, 2.7 Hz, 1H), 3.84 (dd, *J* = 10.9, 2.8 Hz, 1H), 3.80 (s, 3H), 3.69-3.61 (m, 2H), 3.51 (ddd, *J* = 10.8, 9.3, 5.0 Hz, 1H), 3.41-3.31 (m, 2H), 3.17 (dd, *J* = 12.4, 3.8 Hz, 1H), 2.77 (dd, *J* = 16.2, 5.5 Hz, 1H), 2.67-2.59 (m, 1H), 2.33 (dd, *J* = 16.2, 11.6 Hz, 1H), 2.24 (app dt, *J* = 11.7, 4.2 Hz, 1H), 2.11 (app quintet, *J* = 7.4 Hz, 1H), 1.88 (dd, *J* = 11.6, 5.0 Hz, 1H), 1.63 (app q, *J* = 11.8 Hz, 1H), 1.53 (app t, *J* = 11.2 Hz, 1H), 1.06 (s, 9H), 0.85 (s, 3H).

^{13}C (125 MHz, $CDCl_3$): δ 204.6, 159.4, 136.2, 136.1, 135.0, 133.9, 130.1, 130.0, 129.6, 127.9, 127.8, 117.0, 114.0, 83.6, 83.2, 78.7, 77.0, 73.5, 73.4, 70.5, 68.4, 55.5, 46.8, 45.6, 36.1, 30.8, 27.2, 19.5, 15.5.

HR-MS (DART) *m/z* calcd for $C_{40}H_{50}O_7Si$ $(M+H)^+$: 671.3404, found 671.3425.



59

Ketone 59: Powdered 4 Å molecular sieves (64 mg) were flame-dried, then cooled. These were added to a sample of ketone **58** (43 mg, 0.064 mmol). CH_2Cl_2 (1.28 mL) was added to dissolve ketone **58**, and the solution was cooled to -78 °C. A solution of $TMSCHN_2$ (2 M in hexanes, 80 μL, 0.16 mmol) was then added, followed by BF_3•OEt_2 (20 μL, 23 mg, 0.16 mmol), to give a bright yellow solution. The reaction was stirred 2 h. at -78 °C, then quenched at low temperature by addition of sat. $NaHCO_{3(aq)}$ (~ 1 mL). The mixture was then allowed to warm to ambient temperature and extracted. The aqueous layer was extracted further with Et_2O (4 x ~3 mL). The combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was then purified by column chromatography to provide the ring-expanded α-silyl ketone product **63** (21.7 mg, 0.0287 mmol, 45%, R_f = 0.64 (20% EtOAc in hexanes)) and THF **62** (17.4 mg, 0.0273 mmol, 43%, R_f = 0.07 (20% EtOAc in hexanes), 0.33 (30% EtOAc in hexanes)).

The sample of α-silyl ketone **63** collected above (21.7 mg, 0.0287 mmol) was dissolved in MeOH/CH_2Cl_2 (1:1 v/v, 1.44 mL). Pyridinium *p*-toluenesulfonate (PPTS, 18.0 mg, 0.72 mmol) was added, and the reaction solution was stirred at ambient temperature for 5.5 h. It was then quenched by addition of Et_3N (20 μL, 15 mg, 0.144 mmol). The quenched solution was stirred at room temperature for 3 min., then concentrated *in vacuo* and purified by column chromatography (gradient 7% to 60% EtOAc in hexanes) to provide ketone **59** (15.3 mg, 0.0223 mmol, 35% over 2 steps, R_f = 0.67 (30% EtOAc in hexanes)).

$[\alpha]^{22}_D$ = +2.5 (*c* = 0.34, CH_2Cl_2).

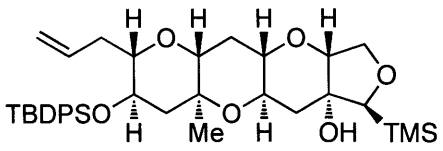
IR (thin film, NaCl): 3071, 2931, 2858, 1717, 1613, 1513, 1463, 1428, 1362, 1303, 1248, 1173, 1105, 1082, 1048 cm^{-1}.

^1H (600 MHz, $CDCl_3$): δ 7.70-7.64 (m, 4H), 7.47-7.42 (m, 2H), 7.42-7.36 (m, 4H), 7.18 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 5.86-5.78 (m, 1H), 5.03-4.97 (m, 2H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 3.93 (app t, *J* = 3.5 Hz, 1H), 3.80 (s, 3H), 3.71-3.65 (m, 2H), 3.58 (app td, *J* = 10.1, 4.2 Hz, 1H), 3.48 (ddd, *J* = 10.8, 9.4, 4.9 Hz, 1H), 3.33 (app td, *J* = 8.6, 2.6 Hz, 1H), 3.03 (dd, *J* = 12.6, 3.9 Hz, 1H), 2.99 (ddd, *J* = 11.1, 9.8, 5.1 Hz, 1H), 2.89 (ddd, *J* = 14.3, 12.1, 2.2 Hz, 1H), 2.65-2.89 (m, 1H), 2.41

(ddd, J = 12.3, 7.1, 1.3 Hz, 1H), 2.12 (app dt, J = 12.0, 4.4 Hz, 1H), 2.07 (app quintet, J = 7.4 Hz, 1H), 2.02-1.96 (m, 1H), 1.85 (dd, J = 11.6, 4.9 Hz, 1H), 1.69 (app q, J = 12.0 Hz, 1H), 1.54-1.40 (m, 2H), 1.05 (s, 9H), 0.85 (s, 3H).

^{13}C (125 MHz, $CDCl_3$): δ 214.8, 159.4, 136.2, 136.1, 135.1, 134.0, 133.4, 130.1, 129.9, 129.4, 127.8, 127.8, 116.8, 113.9, 87.3, 83.4, 82.6, 78.5, 73.4, 72.9, 72.7, 71.4, 70.7, 55.5, 46.9, 38.7, 36.1, 32.4, 30.0, 27.2, 19.5, 15.4.

HR-MS (ESI) *m/z* calcd for $C_{41}H_{52}O_7Si$ $(M+Na)^+$: 707.3375, found 707.3387



62

THF 62: For the preparation of **62**, see the procedure for preparation of ketone **59** above.

R_f = 0.07 (20% EtOAc in hexanes), 0.33 (30% EtOAc in hexanes).

$[\alpha]^{22}_D$ = -14.8 (c = 0.71, CH_2Cl_2)

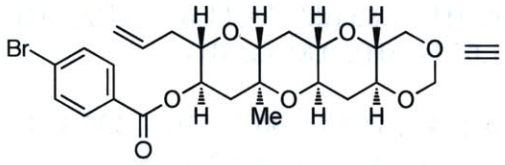
IR (thin film, NaCl): 3404, 3072, 2953, 2896, 2858, 1642, 1590, 1463, 1428, 1378, 1250, 1112, 1075, 1011 cm^{-1}.

^{1}H (600 MHz, $CDCl_3$): δ 7.72-7.64 (m, 4H), 7.47-7.36 (m, 6H), 5.81 (dddd, J = 17.3, 10.6, 6.8 Hz, 1H), 5.02-4.96 (m, 2H), 4.10 (dd, J = 10.2, 4.4 Hz, 1H), 3.82 (app d, J = 10.3 Hz, 1H), 3.79 (d, J = 4.4 Hz, 1H), 3.51-3.46 (m, 2H), 3.41-3.34 (m, 2H), 3.14 (dd, J = 12.4, 3.8 Hz, 1H), 3.09 (ddd, J = 11.2, 9.7, 4.7 Hz, 1H), 2.64-2.58 (m, 1H), 2.34 (dd, J = 13.0, 4.5 Hz, 1H), 2.11-2.04 (m, 2H), 1.93-1.88 (m, 2H), 1.68 (app t, J = 12.3 Hz, 1H), 1.56 (app t, J = 11.3 Hz, 1H), 1.50 (app q, J = 11.9 Hz, 1H), 1.05 (s, 9H), 0.84 (s, 3H), 0.13 (s, 3H).

^{13}C (125 MHz, $CDCl_3$): δ 136.2, 136.1, 135.0, 133.9, 133.4, 130.1, 129.9, 127.9, 127.8, 116.9, 86.1, 85.0, 83.5, 81.8, 78.9, 76.5, 73.6, 72.5, 70.7, 66.8, 46.8, 36.9, 36.1, 30.7, 27.2, 19.5, 16.0, -1.4.

HR-MS (ESI) *m/z* calcd for $C_{36}H_{52}O_6Si_2$ $(M+Na)^+$: 659.3195, found 659.3182.

X-Ray Crystallographic Data for Tetracycle 56:



56

The sample is saved on MIT's Reciprocal Net server as sample #11014. All thermal ellipsoid images were generated using Ortep-3 for Windows v. 2.02. All displacement ellipsoids are scaled to 50% probability.

Figure 1. "Overhead" view of **56**.

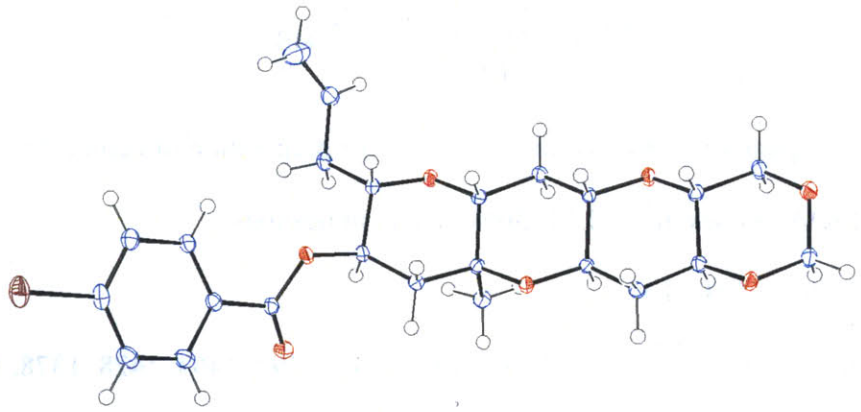


Figure 2. "Side-on" view A of **56**.

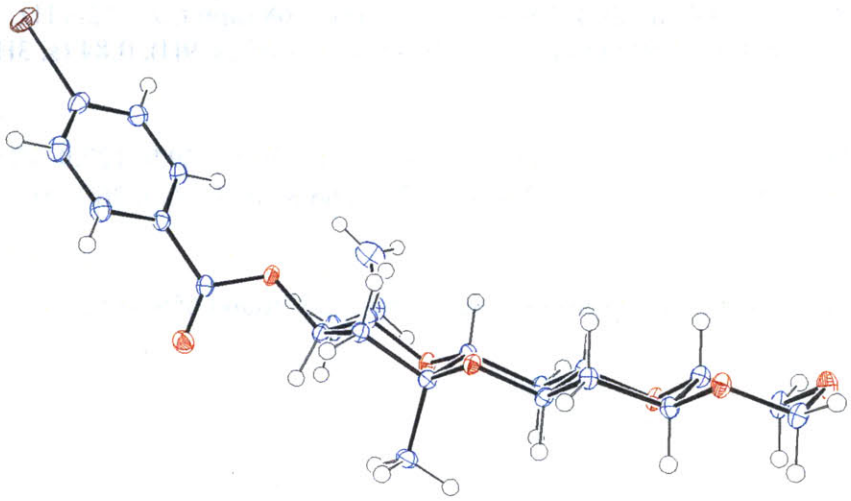


Figure 3. "Side-on" view B of **56**.

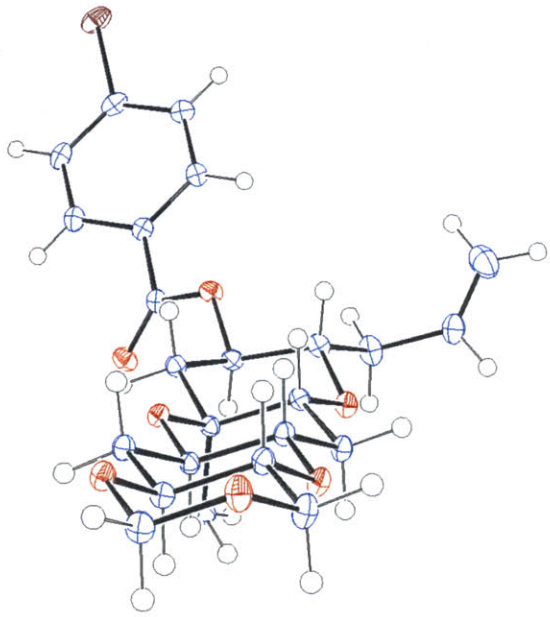


Table 1. Crystal data and structure refinement for 11014.

Identification code	11014	
Empirical formula	C24 H29 Br O7	
Formula weight	509.38	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.3092(6) Å	a= 90°.
	b = 6.2389(4) Å	b= 97.1080(10)°.
	c = 19.7787(12) Å	g = 90°.
Volume	1139.90(12) $Å^3$	
Z	2	
Density (calculated)	1.484 Mg/m^3	
Absorption coefficient	1.846 mm^{-1}	
F(000)	528	
Crystal size	0.35 x 0.20 x 0.10 mm^3	
Theta range for data collection	2.08 to 30.31°.	
Index ranges	-13<=h<=13, -8<=k<=8, -28<=l<=28	
Reflections collected	31760	
Independent reflections	6819 [R(int) = 0.0460]	
Completeness to theta = 30.31°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8369 and 0.5643	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6819 / 1 / 290	
Goodness-of-fit on F^2	1.042	
Final R indices [I>2sigma(I)]	R1 = 0.0280, wR2 = 0.0647	
R indices (all data)	R1 = 0.0324, wR2 = 0.0665	

Absolute structure parameter	-0.007(4)
Largest diff. peak and hole	0.404 and -0.212 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 11014. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	8383(1)	-780(1)	4786(1)	26(1)
C(1)	7158(2)	719(3)	5326(1)	18(1)
C(2)	5964(2)	-360(3)	5518(1)	17(1)
C(3)	5096(2)	696(3)	5937(1)	15(1)
C(4)	5407(2)	2791(3)	6145(1)	14(1)
C(5)	6602(2)	3850(3)	5935(1)	18(1)
C(6)	7488(2)	2803(3)	5526(1)	20(1)
C(7)	4480(2)	3975(3)	6583(1)	14(1)
O(1)	4363(1)	5901(2)	6602(1)	19(1)
O(2)	3789(1)	2594(2)	6954(1)	15(1)
C(8)	2864(2)	3485(3)	7424(1)	13(1)
C(9)	3786(2)	3959(3)	8102(1)	13(1)
C(10)	2829(1)	4311(3)	8664(1)	12(1)
C(24)	2040(2)	6458(3)	8570(1)	16(1)
O(3)	3800(1)	4297(2)	9295(1)	12(1)
C(11)	3070(1)	4309(3)	9892(1)	12(1)
C(12)	4221(1)	4340(3)	10510(1)	13(1)
C(13)	3450(1)	4152(3)	11136(1)	13(1)
O(4)	4486(1)	3984(2)	11732(1)	14(1)
C(14)	3755(2)	3856(3)	12317(1)	16(1)
O(5)	2877(1)	2005(2)	12311(1)	17(1)
C(15)	1764(2)	2002(3)	11741(1)	17(1)
C(16)	2480(2)	2166(3)	11094(1)	13(1)
O(6)	1401(1)	2323(2)	10512(1)	14(1)
C(17)	2086(2)	2337(3)	9902(1)	12(1)
C(18)	963(2)	2321(3)	9275(1)	14(1)
C(19)	1826(2)	2358(3)	8666(1)	12(1)
O(7)	900(1)	2249(2)	8035(1)	14(1)
C(20)	1733(2)	1732(3)	7488(1)	14(1)
C(21)	698(2)	1466(3)	6835(1)	18(1)
C(22)	-314(2)	-385(3)	6868(1)	20(1)
C(23)	-155(2)	-2268(3)	6595(1)	32(1)

Table 3. Bond lengths [Å] and angles [°] for 11014.

Br(1)-C(1)	1.9013(17)
C(1)-C(6)	1.383(3)
C(1)-C(2)	1.393(2)
C(2)-C(3)	1.392(2)
C(2)-H(2)	0.9500
C(3)-C(4)	1.390(2)
C(3)-H(3)	0.9500
C(4)-C(5)	1.400(2)
C(4)-C(7)	1.493(2)
C(5)-C(6)	1.387(2)
C(5)-H(5)	0.9500
C(6)-H(6)	0.9500
C(7)-O(1)	1.208(2)
C(7)-O(2)	1.3466(19)
O(2)-C(8)	1.4530(18)
C(8)-C(9)	1.529(2)
C(8)-C(20)	1.534(2)
C(8)-H(8)	1.0000
C(9)-C(10)	1.5250(18)
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900
C(10)-O(3)	1.4475(15)
C(10)-C(24)	1.528(2)
C(10)-C(19)	1.536(2)
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
O(3)-C(11)	1.4324(15)
C(11)-C(12)	1.5228(17)
C(11)-C(17)	1.536(2)
C(11)-H(11)	1.0000
C(12)-C(13)	1.5116(18)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-O(4)	1.4314(15)
C(13)-C(16)	1.530(2)
C(13)-H(13)	1.0000
O(4)-C(14)	1.4151(18)
C(14)-O(5)	1.413(2)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
O(5)-C(15)	1.4335(19)
C(15)-C(16)	1.517(2)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-O(6)	1.4330(18)
C(16)-H(16)	1.0000
O(6)-C(17)	1.4333(18)
C(17)-C(18)	1.520(2)
C(17)-H(17)	1.0000
C(18)-C(19)	1.528(2)
C(18)-H(18A)	0.9900
C(18)-H(18B)	0.9900
C(19)-O(7)	1.428(2)

C(19)-H(19)	1.0000
O(7)-C(20)	1.4430(18)
C(20)-C(21)	1.523(2)
C(20)-H(20)	1.0000
C(21)-C(22)	1.497(2)
C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900
C(22)-C(23)	1.308(3)
C(22)-H(22)	0.9500
C(23)-H(23A)	0.9500
C(23)-H(23B)	0.9500

C(6)-C(1)-C(2)	122.18(16)
C(6)-C(1)-Br(1)	119.74(13)
C(2)-C(1)-Br(1)	118.06(13)
C(3)-C(2)-C(1)	118.40(15)
C(3)-C(2)-H(2)	120.8
C(1)-C(2)-H(2)	120.8
C(4)-C(3)-C(2)	120.41(15)
C(4)-C(3)-H(3)	119.8
C(2)-C(3)-H(3)	119.8
C(3)-C(4)-C(5)	120.00(15)
C(3)-C(4)-C(7)	121.54(14)
C(5)-C(4)-C(7)	118.45(15)
C(6)-C(5)-C(4)	120.14(16)
C(6)-C(5)-H(5)	119.9
C(4)-C(5)-H(5)	119.9
C(1)-C(6)-C(5)	118.86(15)
C(1)-C(6)-H(6)	120.6
C(5)-C(6)-H(6)	120.6
O(1)-C(7)-O(2)	124.63(14)
O(1)-C(7)-C(4)	124.91(15)
O(2)-C(7)-C(4)	110.46(15)
C(7)-O(2)-C(8)	117.71(12)
O(2)-C(8)-C(9)	108.74(12)
O(2)-C(8)-C(20)	104.32(12)
C(9)-C(8)-C(20)	112.45(13)
O(2)-C(8)-H(8)	110.4
C(9)-C(8)-H(8)	110.4
C(20)-C(8)-H(8)	110.4
C(10)-C(9)-C(8)	110.63(11)
C(10)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9A)	109.5
C(10)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	108.1
O(3)-C(10)-C(9)	105.64(10)
O(3)-C(10)-C(24)	110.52(14)
C(9)-C(10)-C(24)	110.61(13)
O(3)-C(10)-C(19)	107.96(13)
C(9)-C(10)-C(19)	107.29(14)
C(24)-C(10)-C(19)	114.38(12)
C(10)-C(24)-H(24A)	109.5
C(10)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(10)-C(24)-H(24C)	109.5

H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(11)-O(3)-C(10)	113.63(9)
O(3)-C(11)-C(12)	107.63(10)
O(3)-C(11)-C(17)	110.59(13)
C(12)-C(11)-C(17)	111.17(14)
O(3)-C(11)-H(11)	109.1
C(12)-C(11)-H(11)	109.1
C(17)-C(11)-H(11)	109.1
C(13)-C(12)-C(11)	107.38(10)
C(13)-C(12)-H(12A)	110.2
C(11)-C(12)-H(12A)	110.2
C(13)-C(12)-H(12B)	110.2
C(11)-C(12)-H(12B)	110.2
H(12A)-C(12)-H(12B)	108.5
O(4)-C(13)-C(12)	109.93(10)
O(4)-C(13)-C(16)	108.61(14)
C(12)-C(13)-C(16)	110.78(14)
O(4)-C(13)-H(13)	109.2
C(12)-C(13)-H(13)	109.2
C(16)-C(13)-H(13)	109.2
C(14)-O(4)-C(13)	109.55(10)
O(5)-C(14)-O(4)	111.98(13)
O(5)-C(14)-H(14A)	109.2
O(4)-C(14)-H(14A)	109.2
O(5)-C(14)-H(14B)	109.2
O(4)-C(14)-H(14B)	109.2
H(14A)-C(14)-H(14B)	107.9
C(14)-O(5)-C(15)	111.70(12)
O(5)-C(15)-C(16)	108.25(12)
O(5)-C(15)-H(15A)	110.0
C(16)-C(15)-H(15A)	110.0
O(5)-C(15)-H(15B)	110.0
C(16)-C(15)-H(15B)	110.0
H(15A)-C(15)-H(15B)	108.4
O(6)-C(16)-C(15)	110.13(12)
O(6)-C(16)-C(13)	109.83(12)
C(15)-C(16)-C(13)	109.02(13)
O(6)-C(16)-H(16)	109.3
C(15)-C(16)-H(16)	109.3
C(13)-C(16)-H(16)	109.3
C(16)-O(6)-C(17)	109.61(11)
O(6)-C(17)-C(18)	110.81(12)
O(6)-C(17)-C(11)	110.15(12)
C(18)-C(17)-C(11)	110.20(12)
O(6)-C(17)-H(17)	108.5
C(18)-C(17)-H(17)	108.5
C(11)-C(17)-H(17)	108.5
C(17)-C(18)-C(19)	105.53(12)
C(17)-C(18)-H(18A)	110.6
C(19)-C(18)-H(18A)	110.6
C(17)-C(18)-H(18B)	110.6
C(19)-C(18)-H(18B)	110.6
H(18A)-C(18)-H(18B)	108.8
O(7)-C(19)-C(18)	111.60(12)
O(7)-C(19)-C(10)	109.74(13)

C(18)-C(19)-C(10)	113.11(13)
O(7)-C(19)-H(19)	107.4
C(18)-C(19)-H(19)	107.4
C(10)-C(19)-H(19)	107.4
C(19)-O(7)-C(20)	110.03(11)
O(7)-C(20)-C(21)	108.52(12)
O(7)-C(20)-C(8)	109.93(12)
C(21)-C(20)-C(8)	112.08(13)
O(7)-C(20)-H(20)	108.7
C(21)-C(20)-H(20)	108.7
C(8)-C(20)-H(20)	108.7
C(22)-C(21)-C(20)	112.54(14)
C(22)-C(21)-H(21A)	109.1
C(20)-C(21)-H(21A)	109.1
C(22)-C(21)-H(21B)	109.1
C(20)-C(21)-H(21B)	109.1
H(21A)-C(21)-H(21B)	107.8
C(23)-C(22)-C(21)	124.84(17)
C(23)-C(22)-H(22)	117.6
C(21)-C(22)-H(22)	117.6
C(22)-C(23)-H(23A)	120.0
C(22)-C(23)-H(23B)	120.0
H(23A)-C(23)-H(23B)	120.0

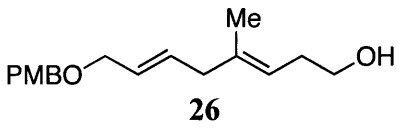
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 11014. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	20(1)	39(1)	21(1)	-4(1)	7(1)	8(1)
C(1)	16(1)	28(1)	12(1)	0(1)	2(1)	5(1)
C(2)	19(1)	19(1)	13(1)	0(1)	1(1)	2(1)
C(3)	17(1)	16(1)	11(1)	1(1)	2(1)	-2(1)
C(4)	14(1)	17(1)	11(1)	2(1)	1(1)	0(1)
C(5)	16(1)	20(1)	18(1)	2(1)	2(1)	-3(1)
C(6)	13(1)	27(1)	20(1)	3(1)	3(1)	-2(1)
C(7)	14(1)	17(1)	10(1)	0(1)	1(1)	-2(1)
O(1)	24(1)	14(1)	19(1)	1(1)	4(1)	-2(1)
O(2)	19(1)	14(1)	12(1)	0(1)	7(1)	0(1)
C(8)	15(1)	13(1)	11(1)	0(1)	4(1)	0(1)
C(9)	14(1)	13(1)	12(1)	-1(1)	3(1)	-2(1)
C(10)	12(1)	12(1)	11(1)	-1(1)	0(1)	0(1)
C(24)	18(1)	13(1)	15(1)	1(1)	0(1)	3(1)
O(3)	11(1)	15(1)	10(1)	0(1)	2(1)	0(1)
C(11)	12(1)	12(1)	11(1)	-2(1)	2(1)	-2(1)
C(12)	12(1)	15(1)	12(1)	1(1)	2(1)	-2(1)
C(13)	13(1)	14(1)	11(1)	1(1)	1(1)	0(1)
O(4)	13(1)	19(1)	10(1)	-1(1)	0(1)	-2(1)
C(14)	17(1)	20(1)	11(1)	-2(1)	2(1)	-2(1)
O(5)	17(1)	22(1)	12(1)	1(1)	-1(1)	-5(1)
C(15)	15(1)	24(1)	12(1)	0(1)	2(1)	-4(1)
C(16)	12(1)	16(1)	11(1)	-1(1)	0(1)	-2(1)
O(6)	12(1)	21(1)	10(1)	-1(1)	2(1)	-2(1)
C(17)	12(1)	15(1)	10(1)	-1(1)	3(1)	-2(1)
C(18)	12(1)	17(1)	12(1)	0(1)	2(1)	-3(1)
C(19)	13(1)	12(1)	10(1)	0(1)	0(1)	-1(1)
O(7)	15(1)	19(1)	9(1)	-1(1)	1(1)	-3(1)
C(20)	17(1)	15(1)	10(1)	-1(1)	2(1)	-2(1)
C(21)	23(1)	22(1)	9(1)	1(1)	0(1)	-6(1)
C(22)	18(1)	25(1)	15(1)	1(1)	0(1)	-5(1)
C(23)	34(1)	24(1)	34(1)	-2(1)	-6(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 11014.

	x	y	z	U(eq)
H(2)	5746	-1783	5368	20
H(3)	4287	-20	6082	18
H(5)	6807	5287	6073	22
H(6)	8306	3507	5386	24
H(8)	2384	4823	7231	15
H(9A)	4451	2744	8225	16
H(9B)	4379	5256	8054	16
H(24A)	1404	6633	8925	24
H(24B)	1460	6494	8121	24
H(24C)	2750	7626	8602	24
H(11)	2468	5636	9892	14
H(12A)	4900	3127	10489	16
H(12B)	4779	5693	10523	16
H(13)	2842	5458	11174	15
H(14A)	4476	3834	12730	19
H(14B)	3144	5145	12341	19
H(15A)	1103	3231	11773	20
H(15B)	1192	663	11737	20
H(16)	3083	860	11049	16
H(17)	2695	1019	9896	14
H(18A)	327	3594	9270	17
H(18B)	357	1015	9266	17
H(19)	2452	1049	8697	14
H(20)	2246	342	7596	17
H(21A)	126	2797	6747	22
H(21B)	1266	1249	6449	22
H(22)	-1132	-177	7103	24
H(23A)	649	-2536	6355	38
H(23B)	-845	-3367	6637	38



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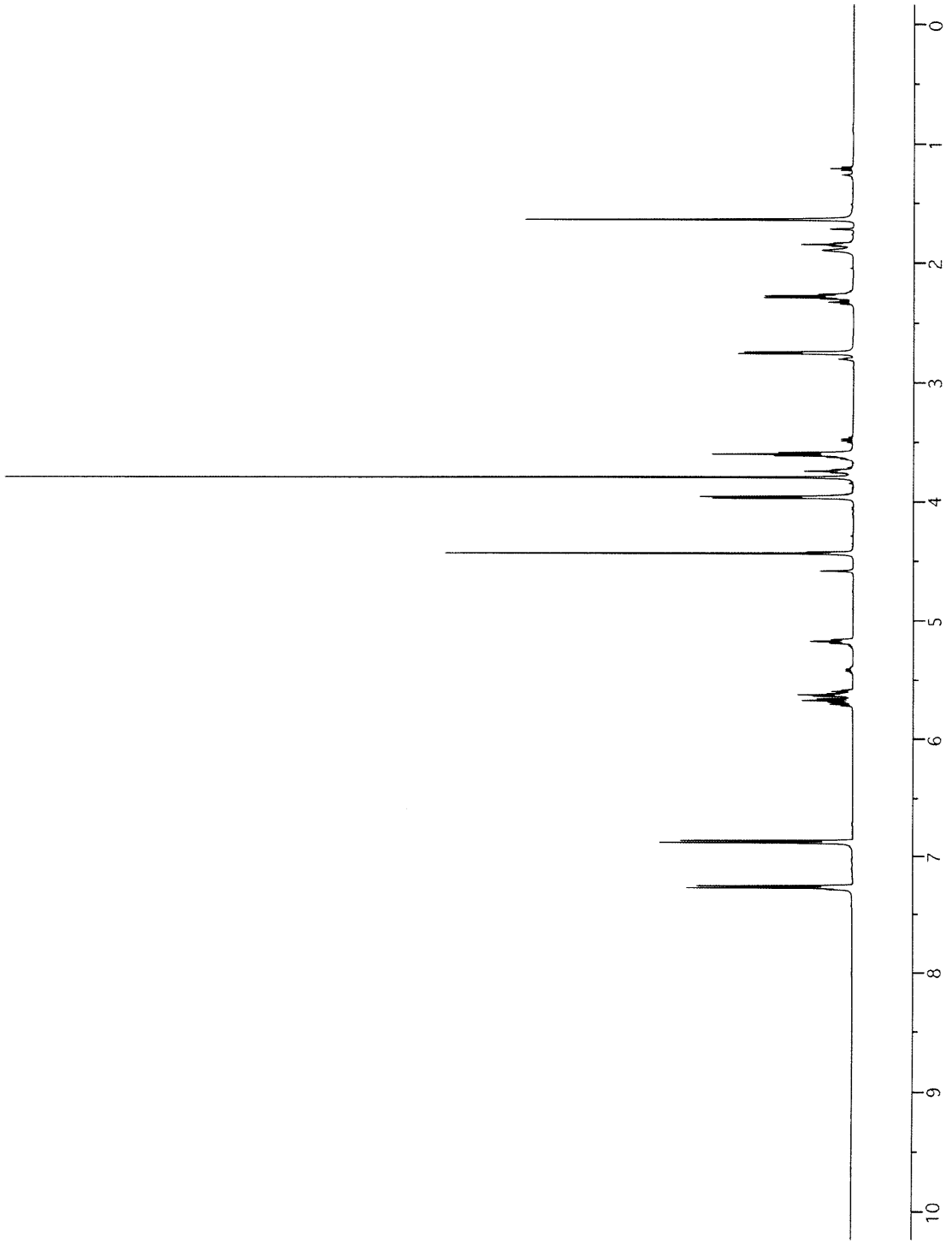

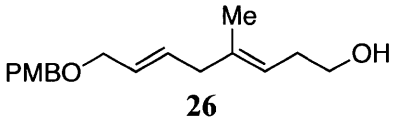

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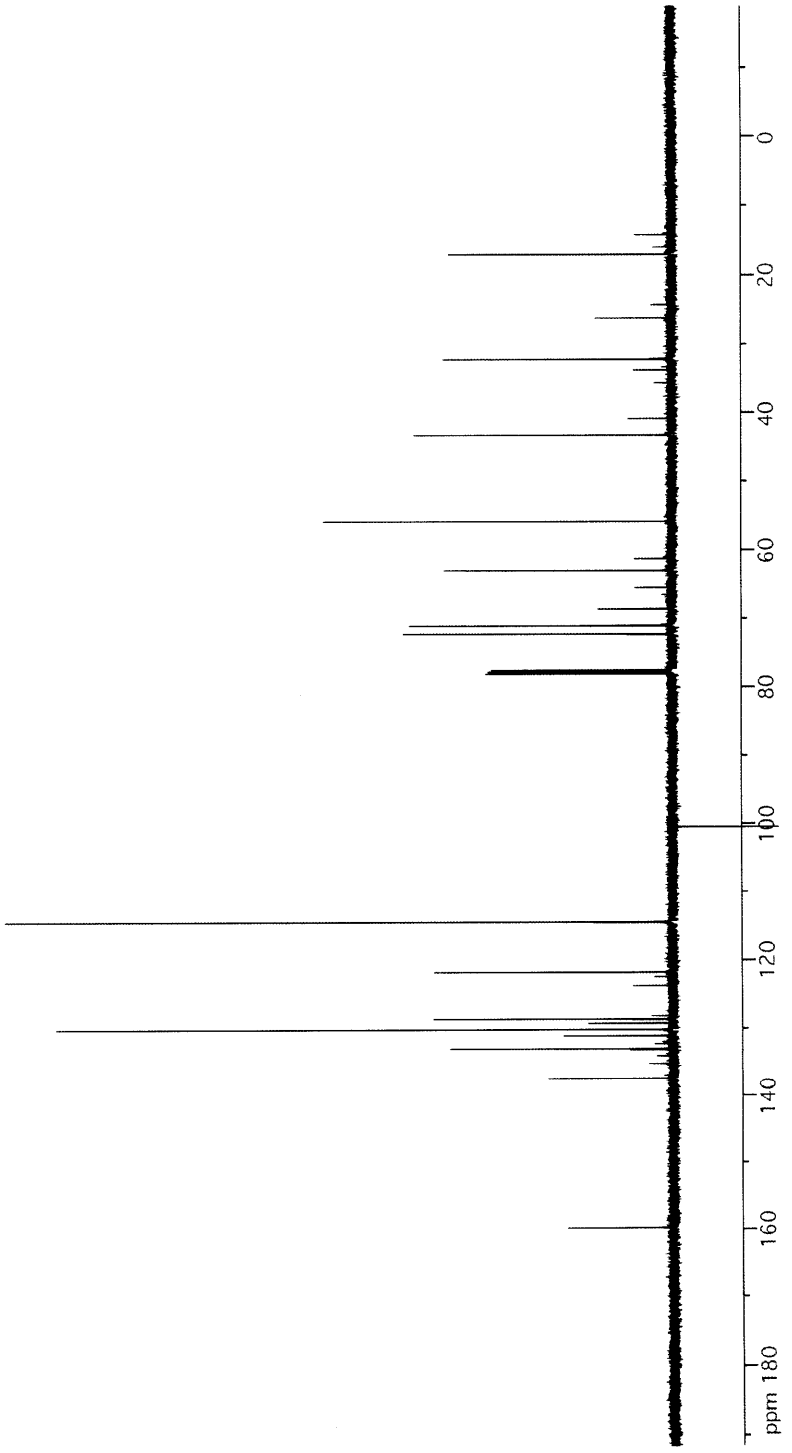

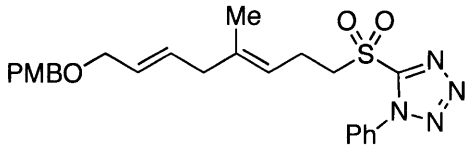

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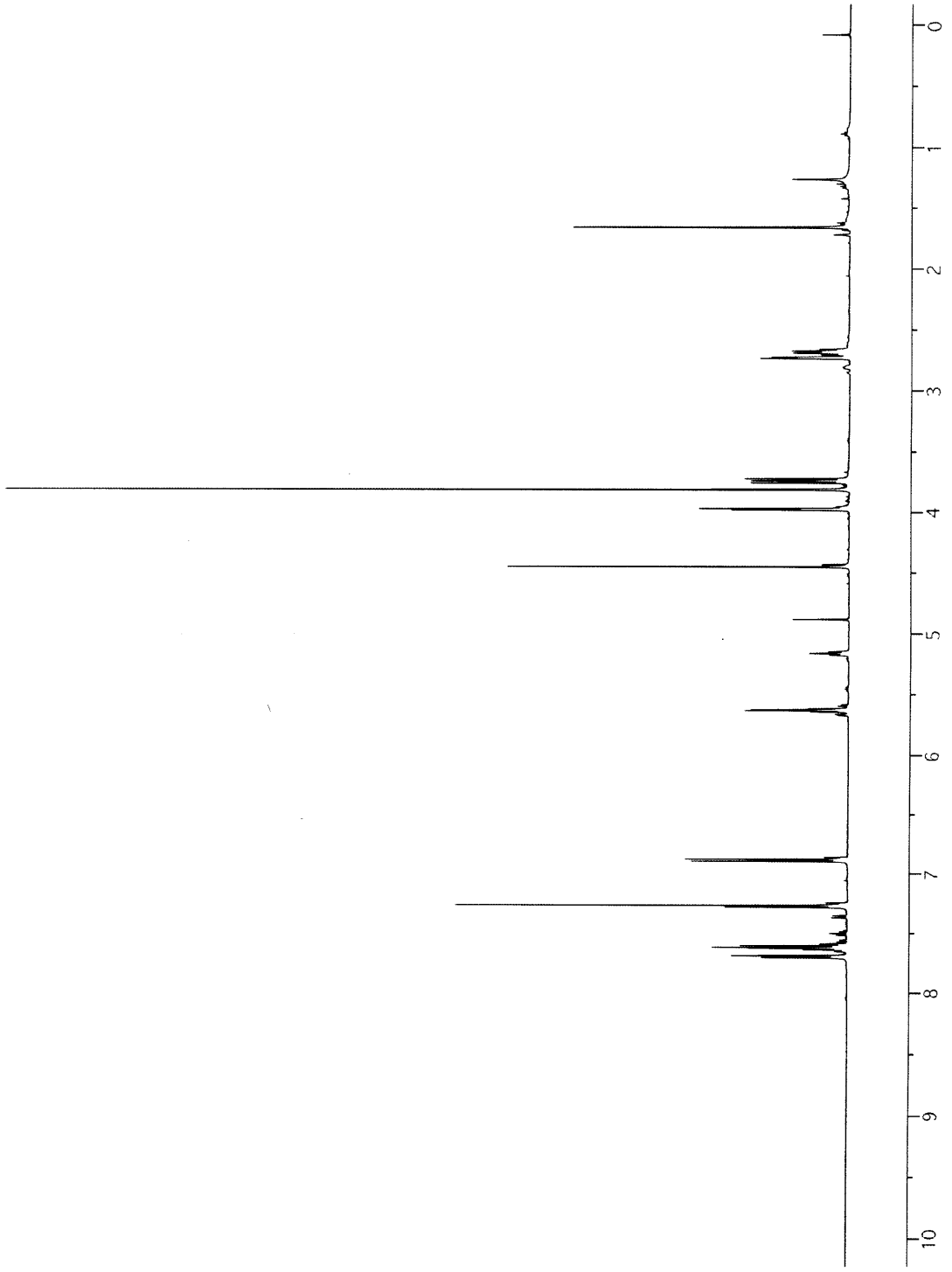

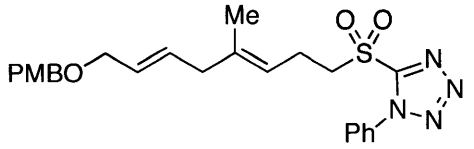

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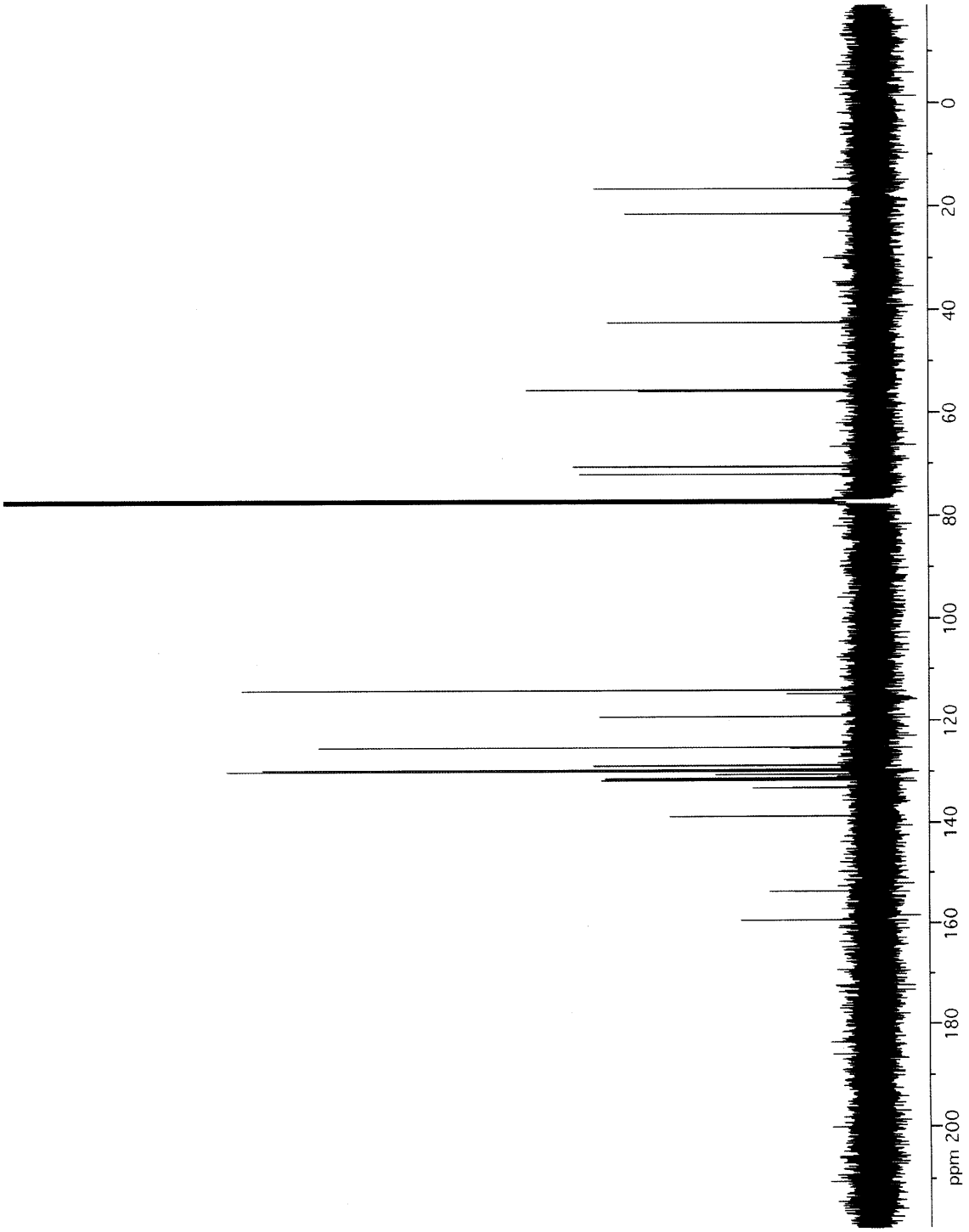

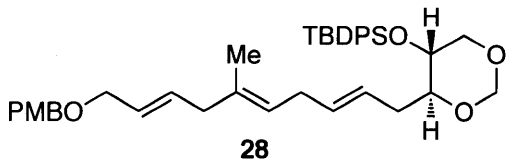

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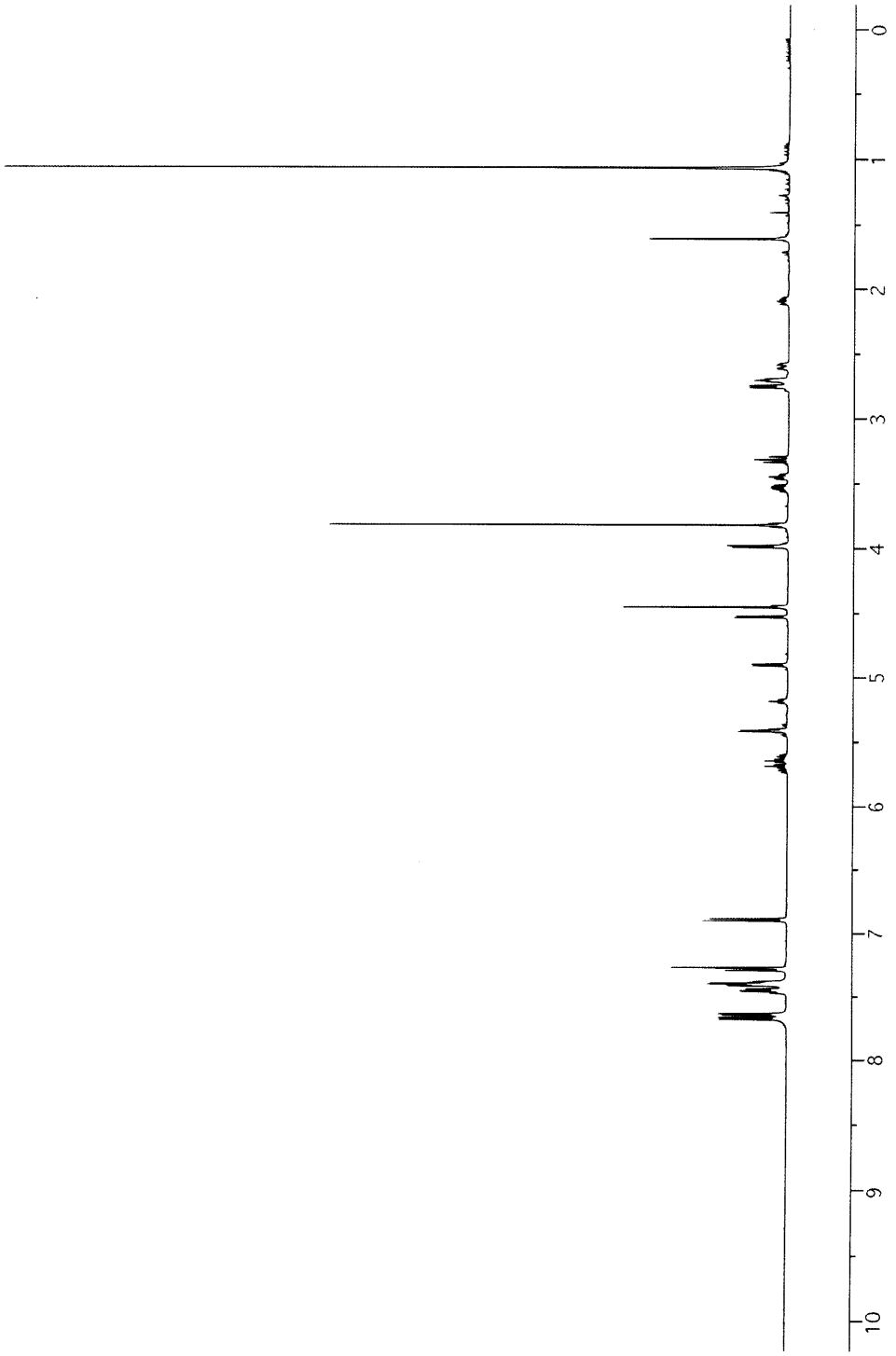

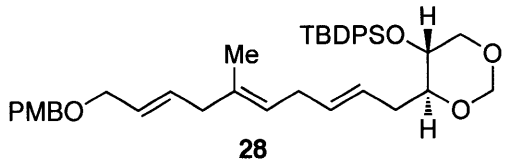
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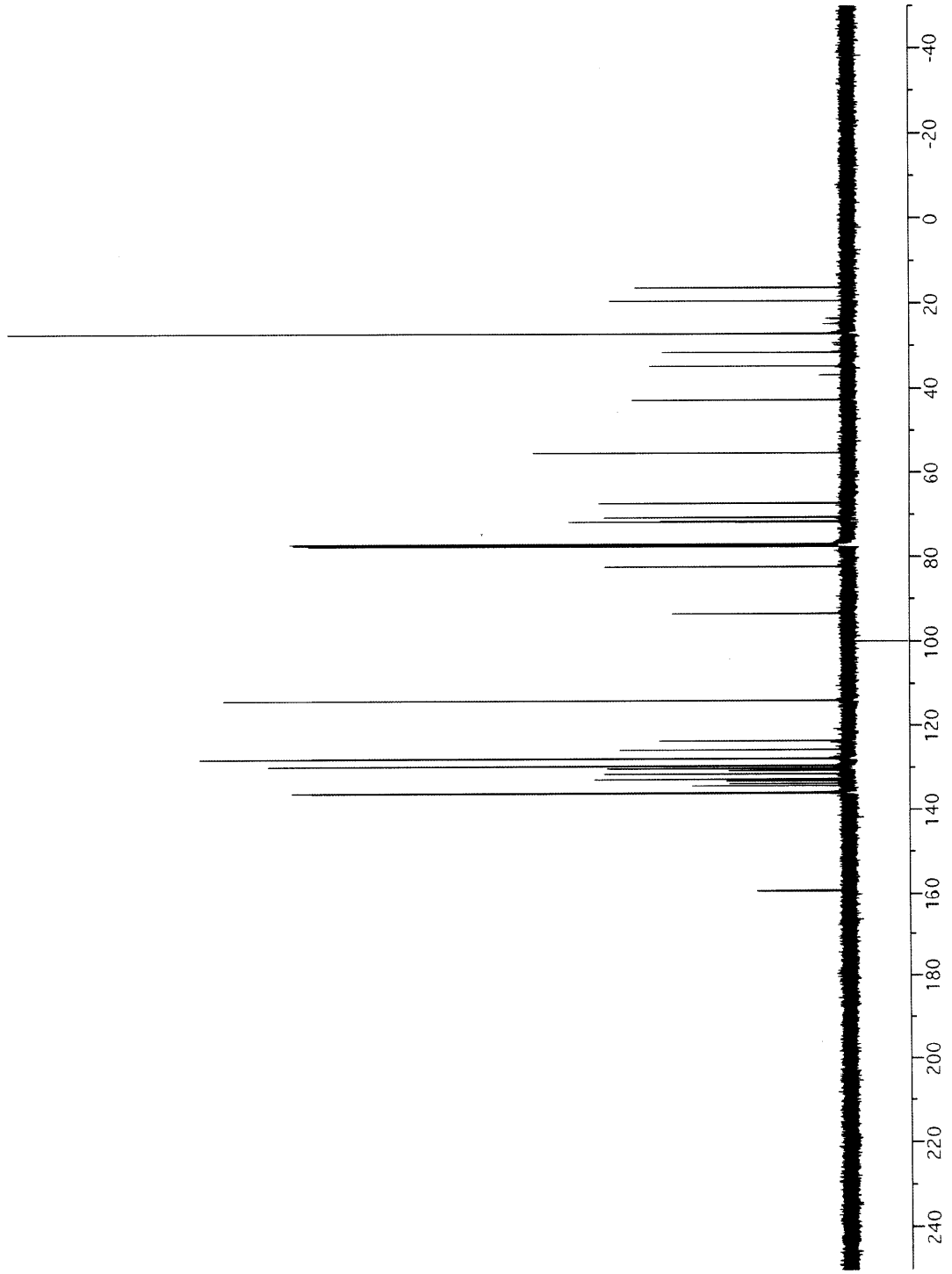
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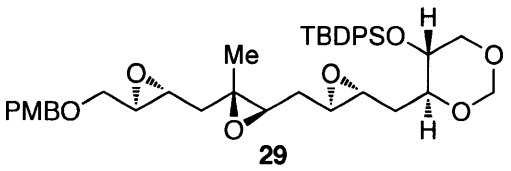

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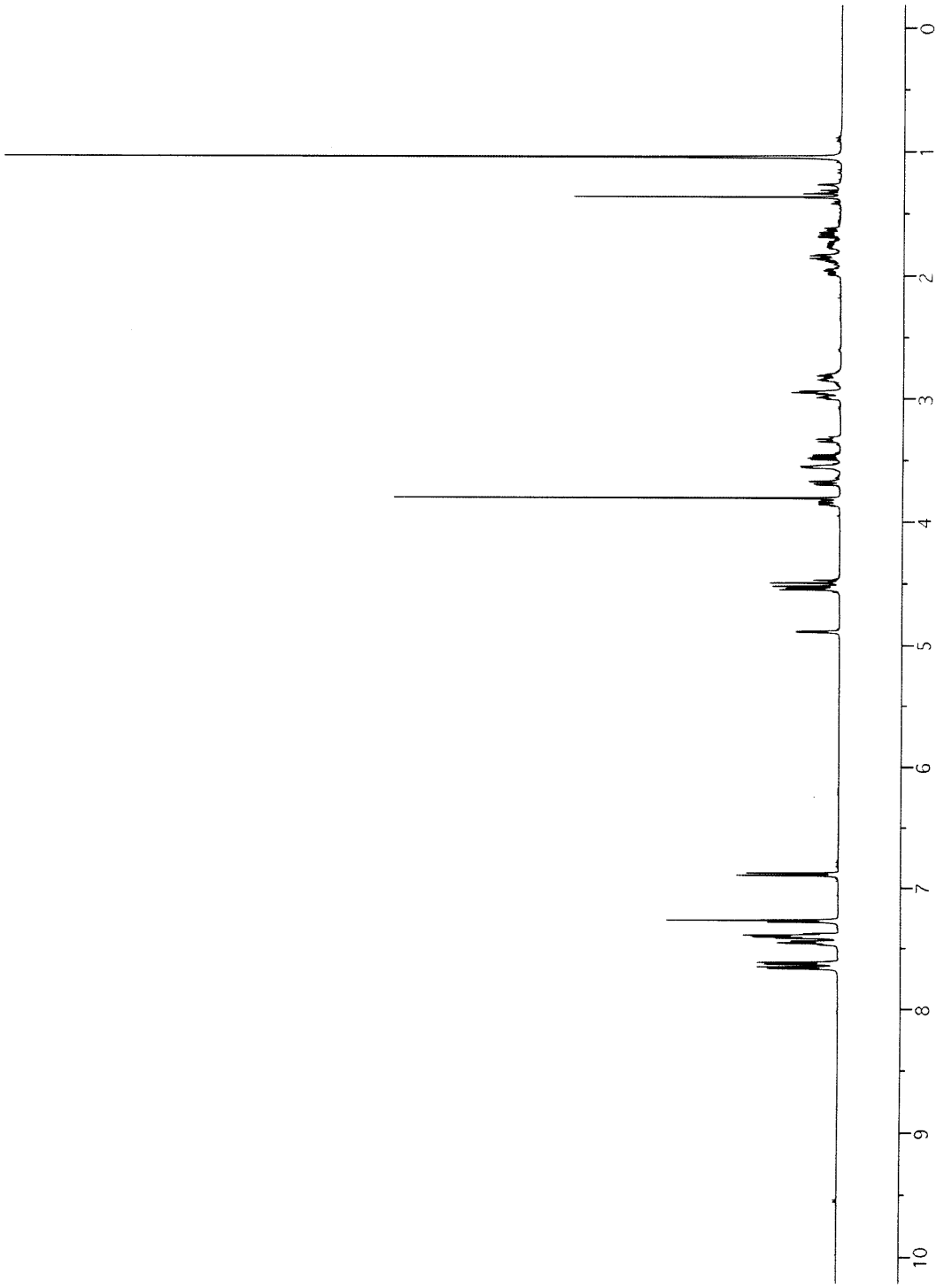

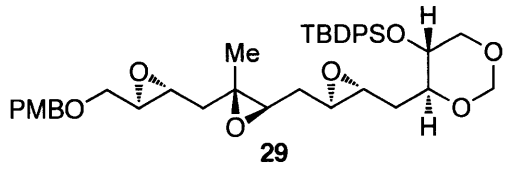
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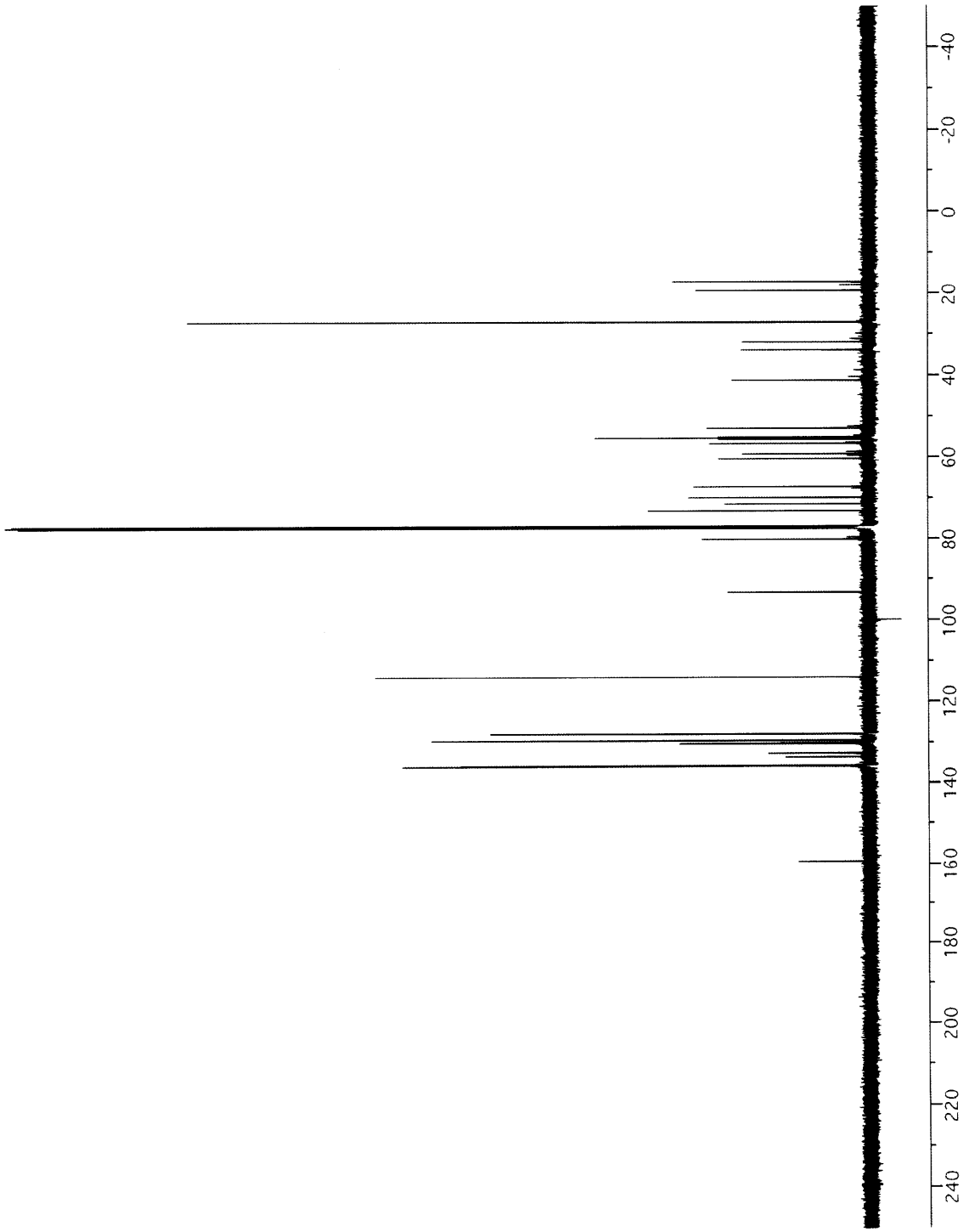
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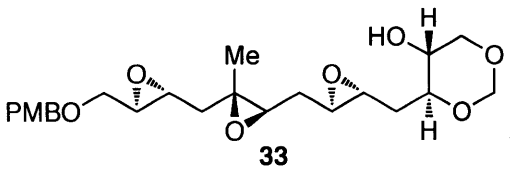

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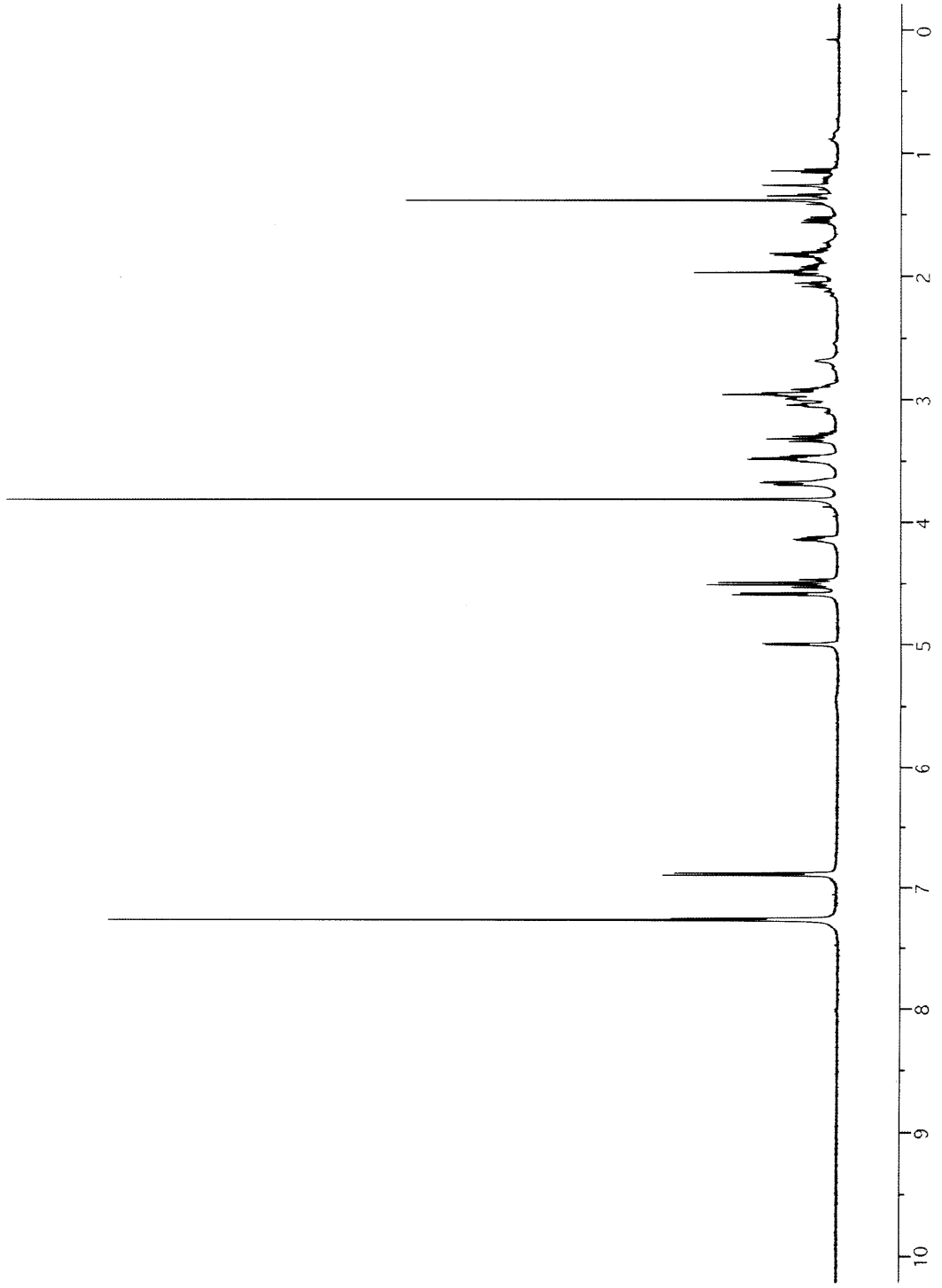

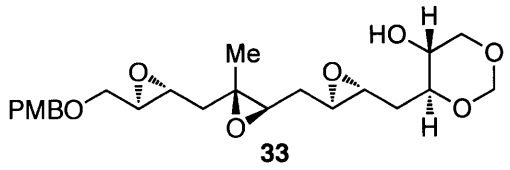
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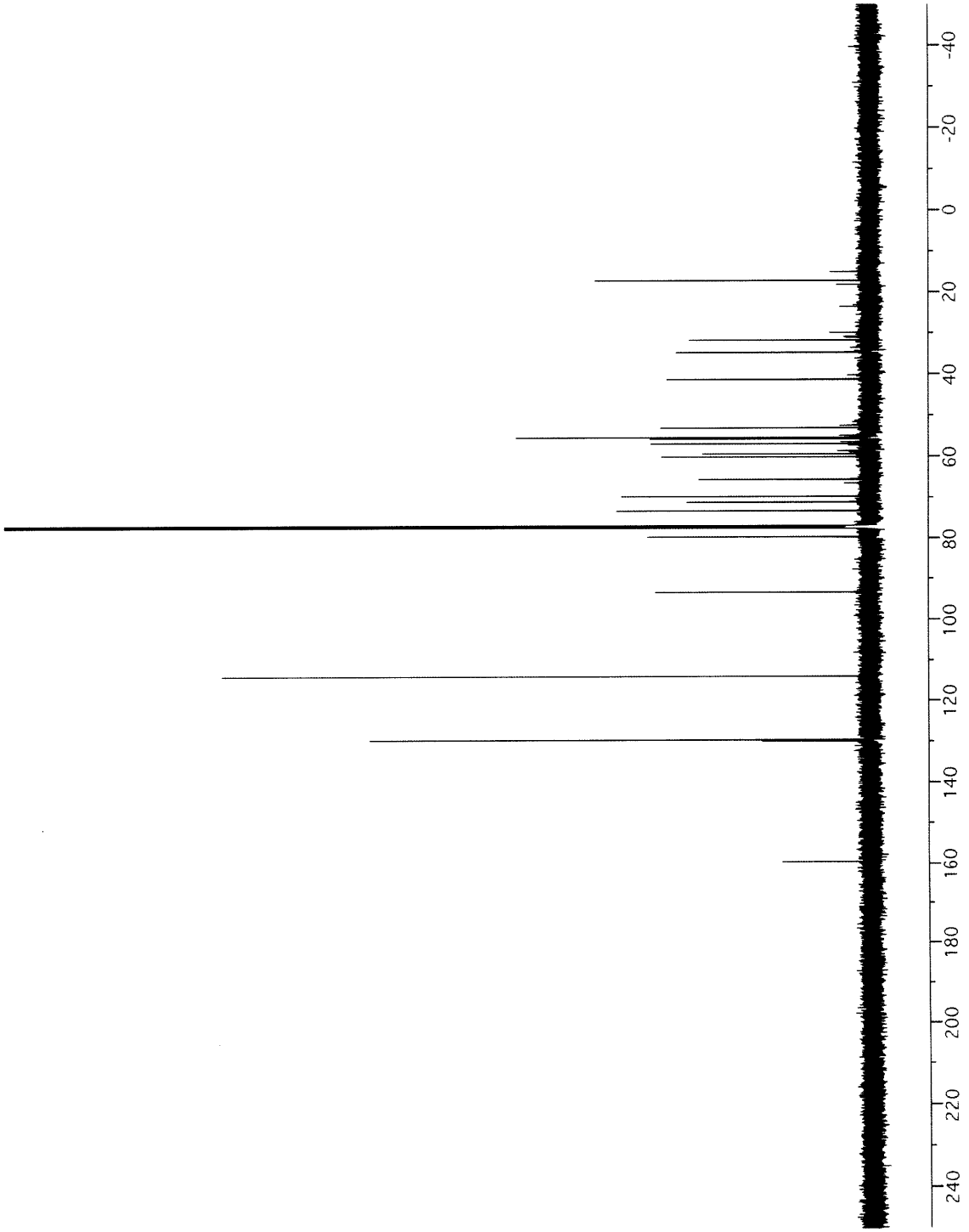
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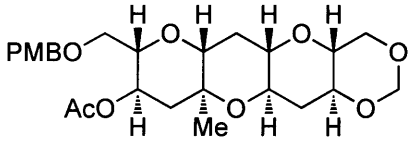

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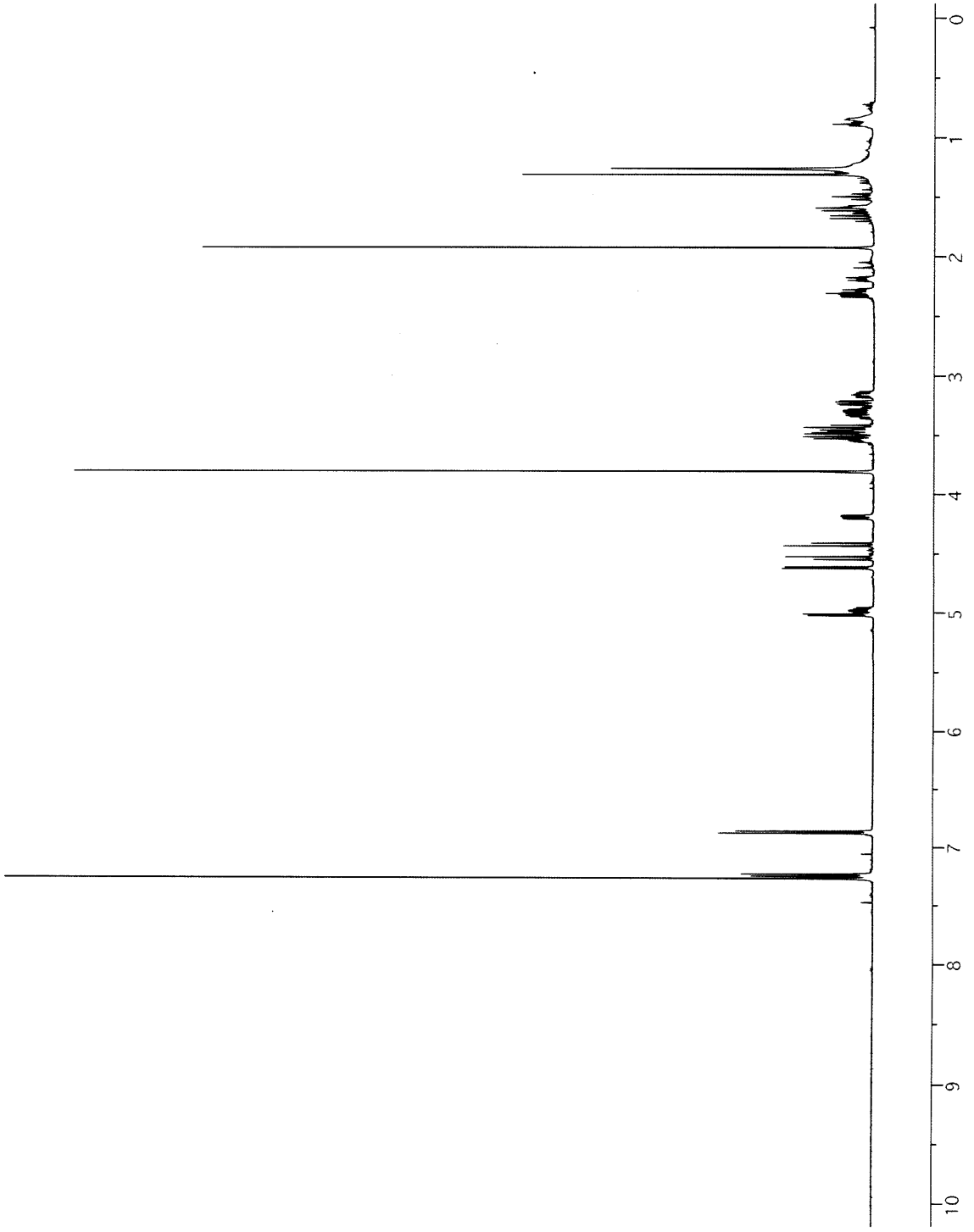

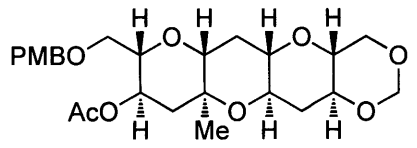

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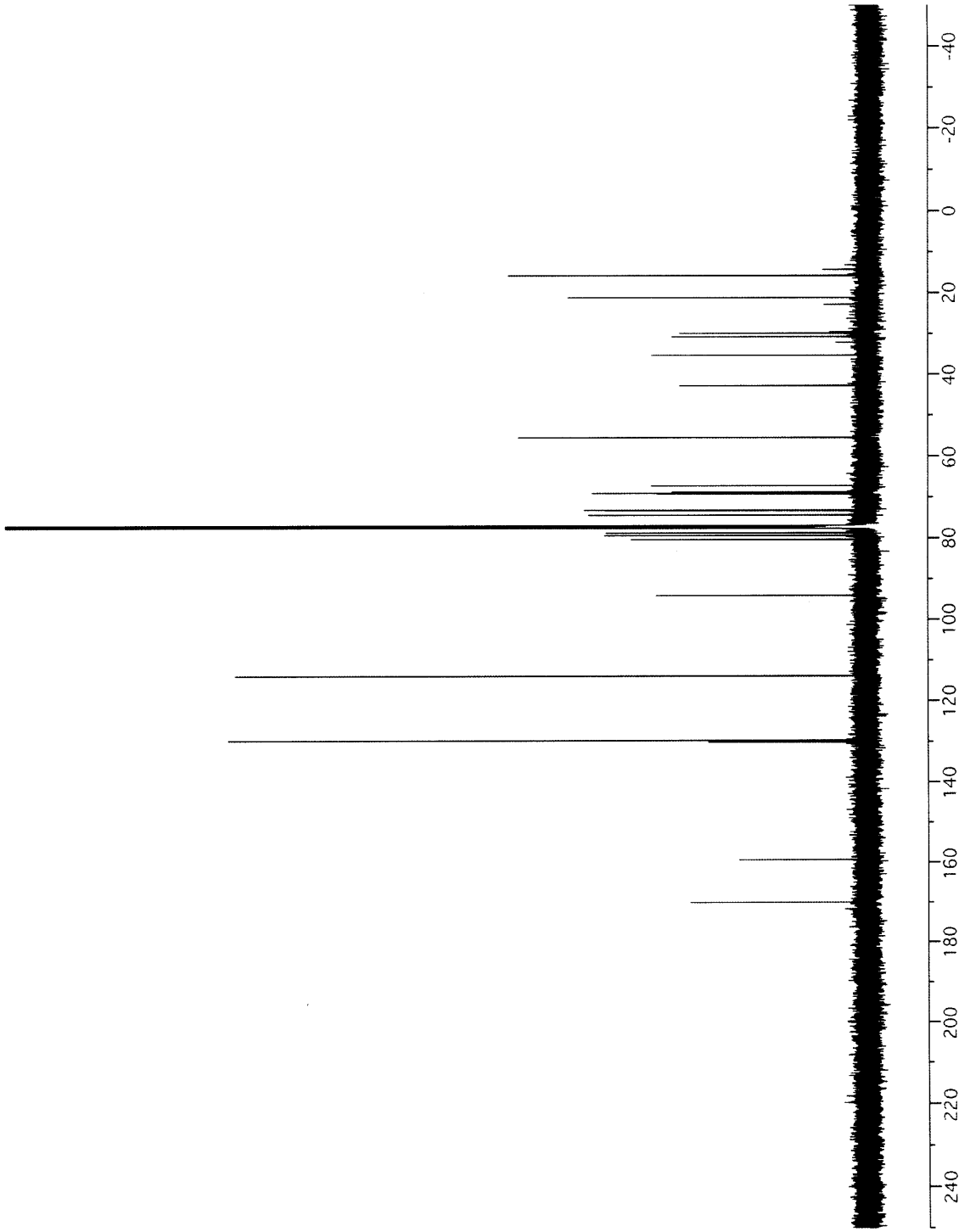

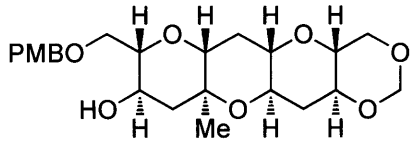

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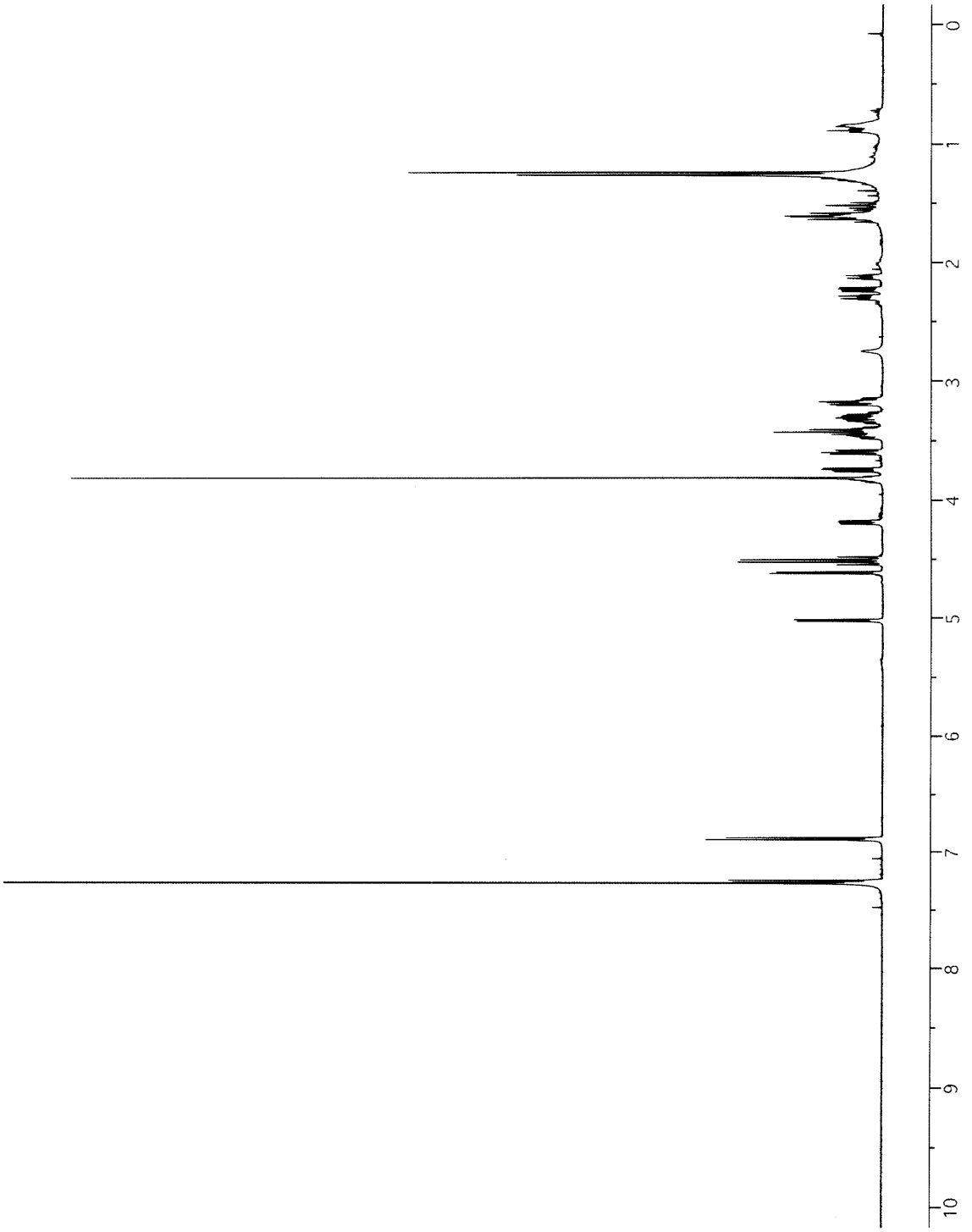

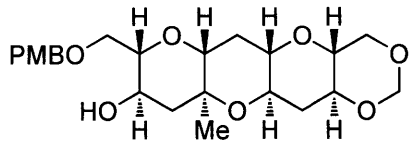
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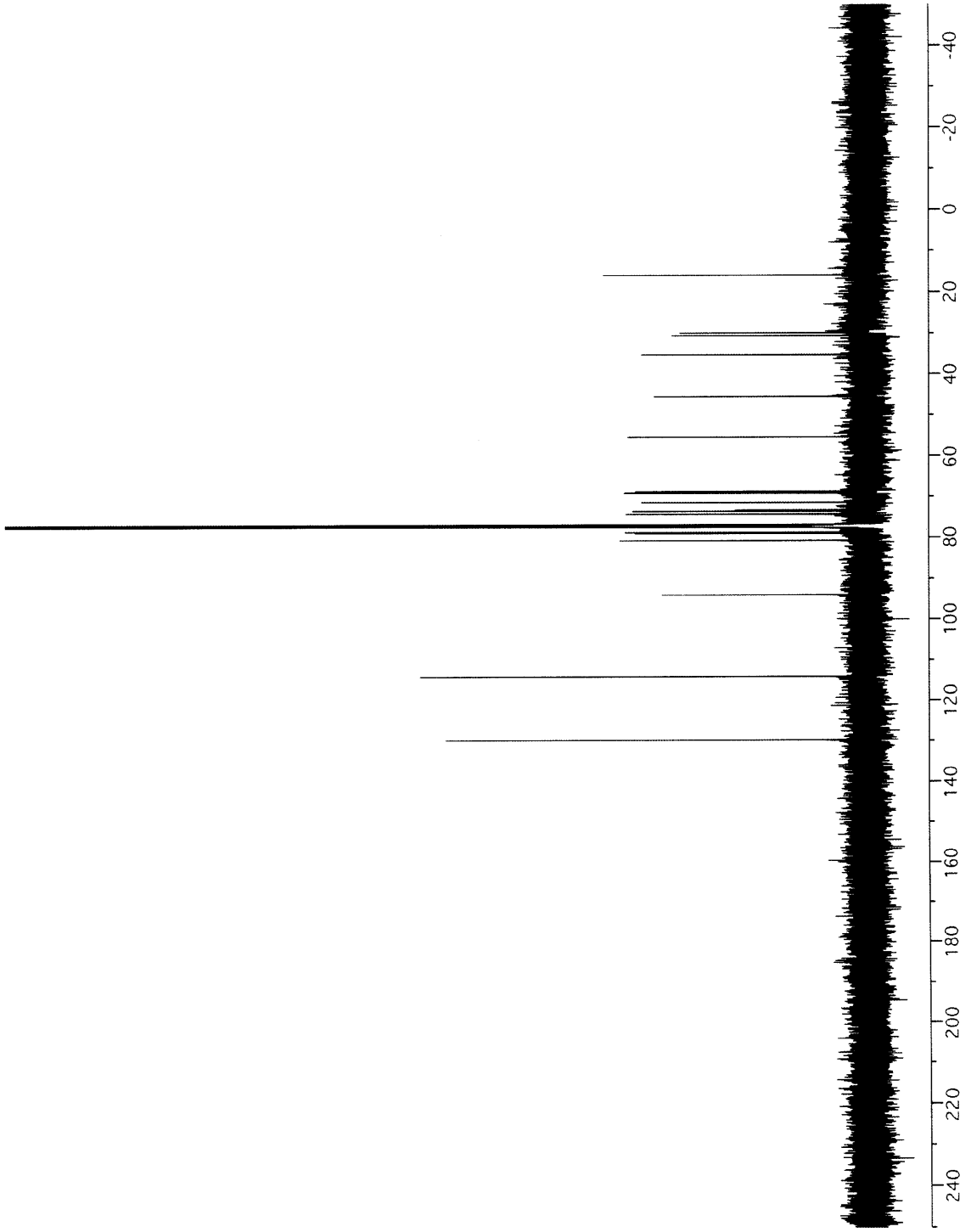
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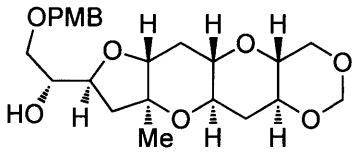

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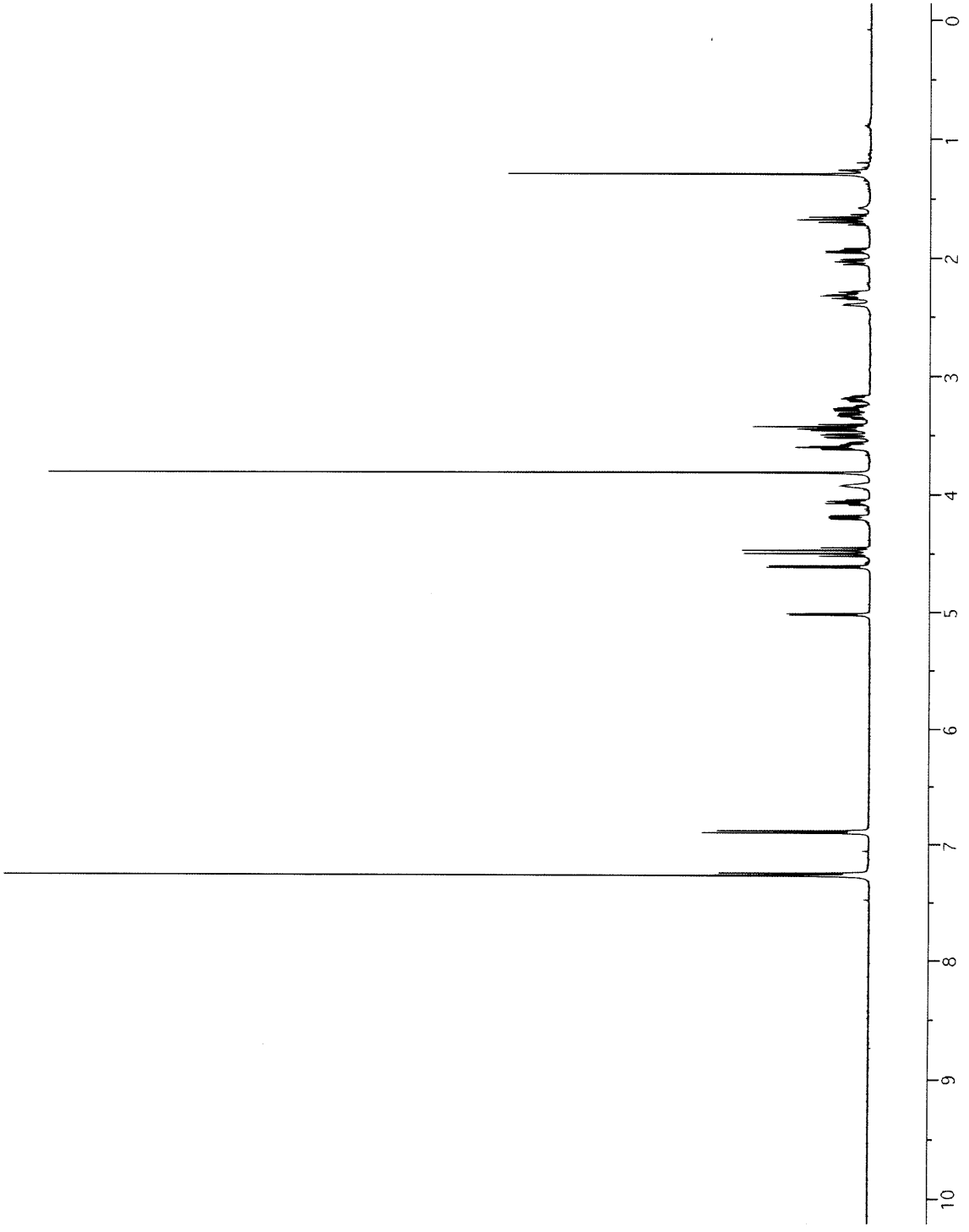

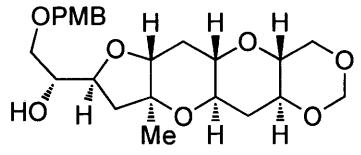
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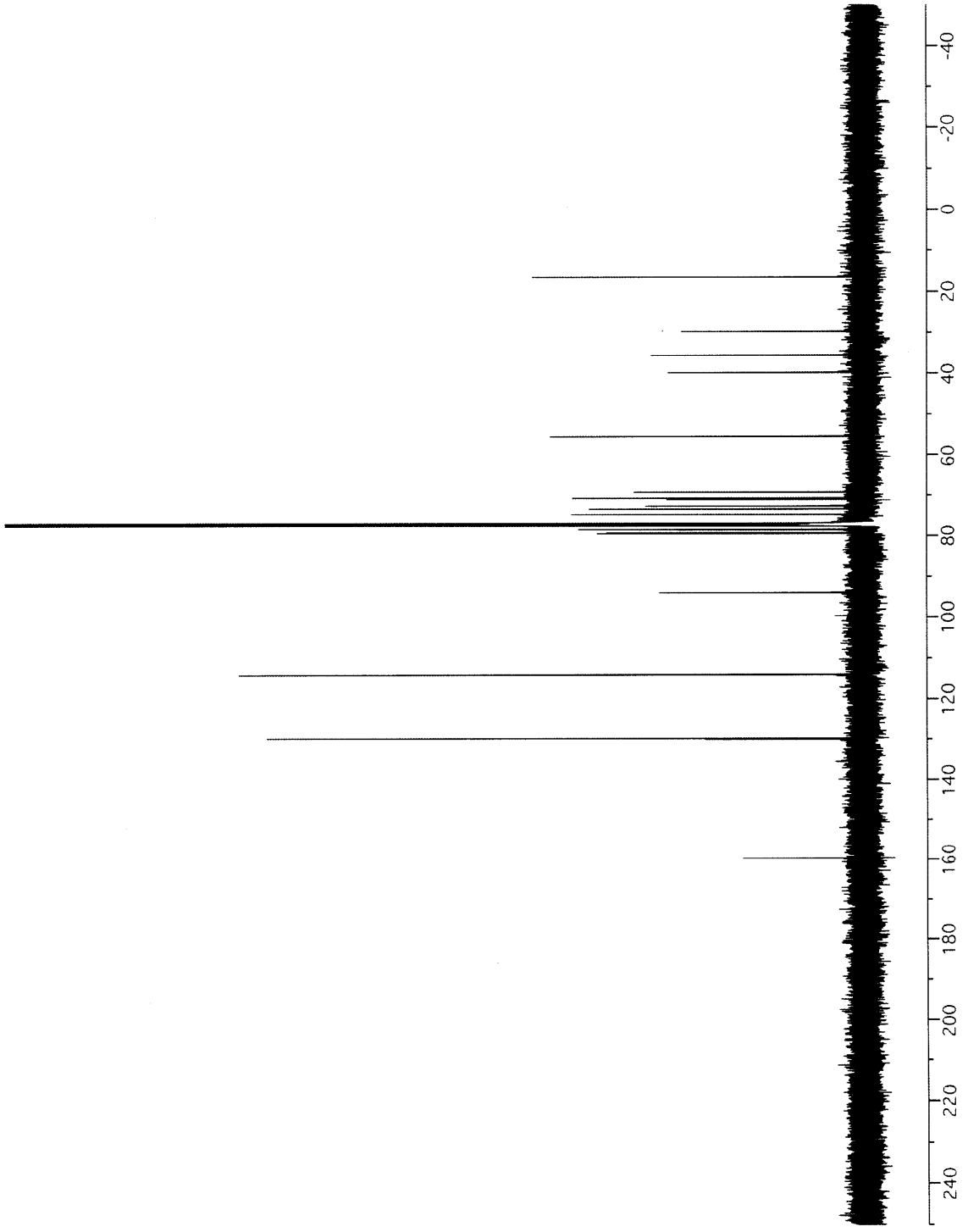
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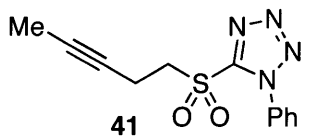

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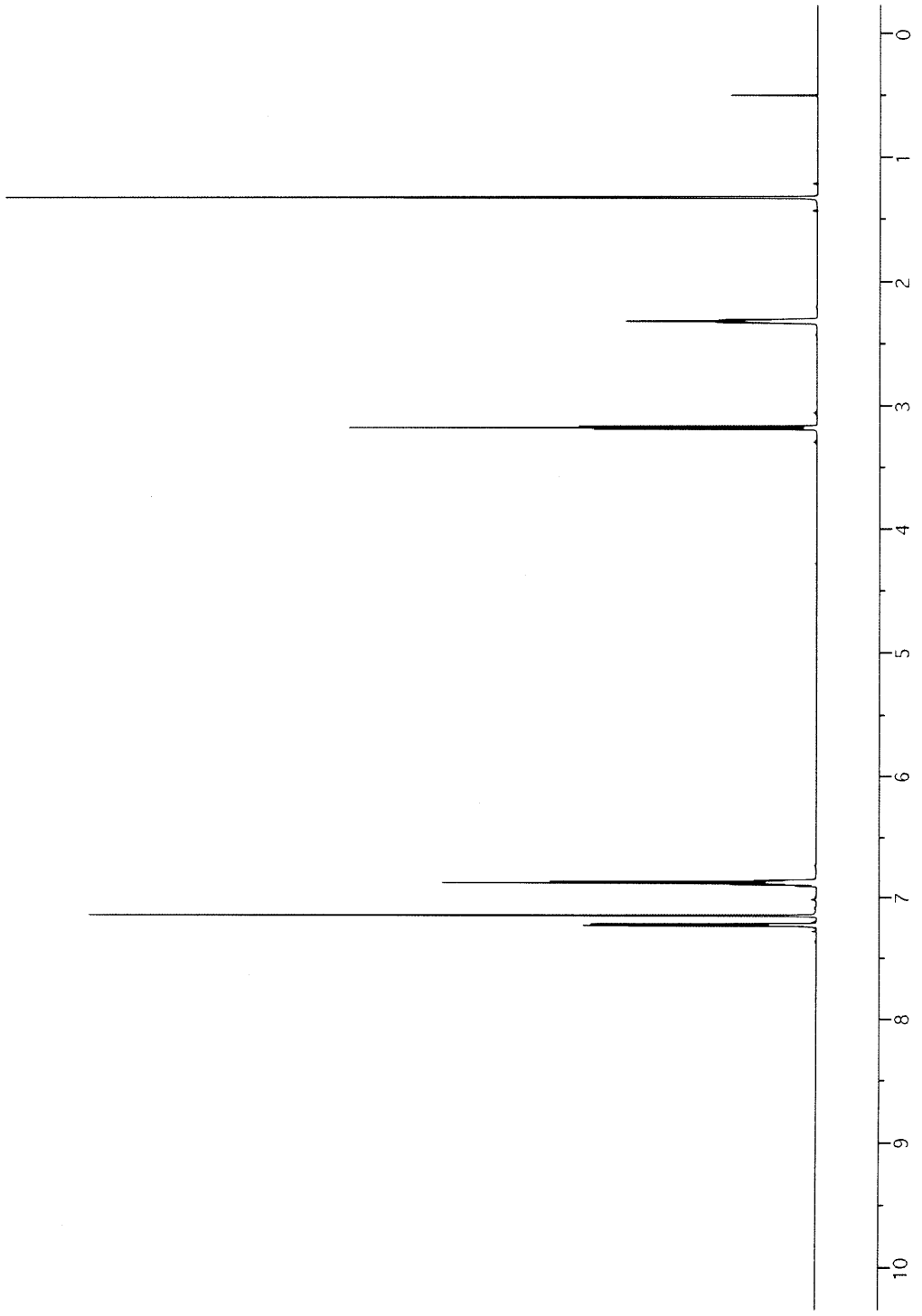

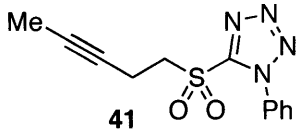

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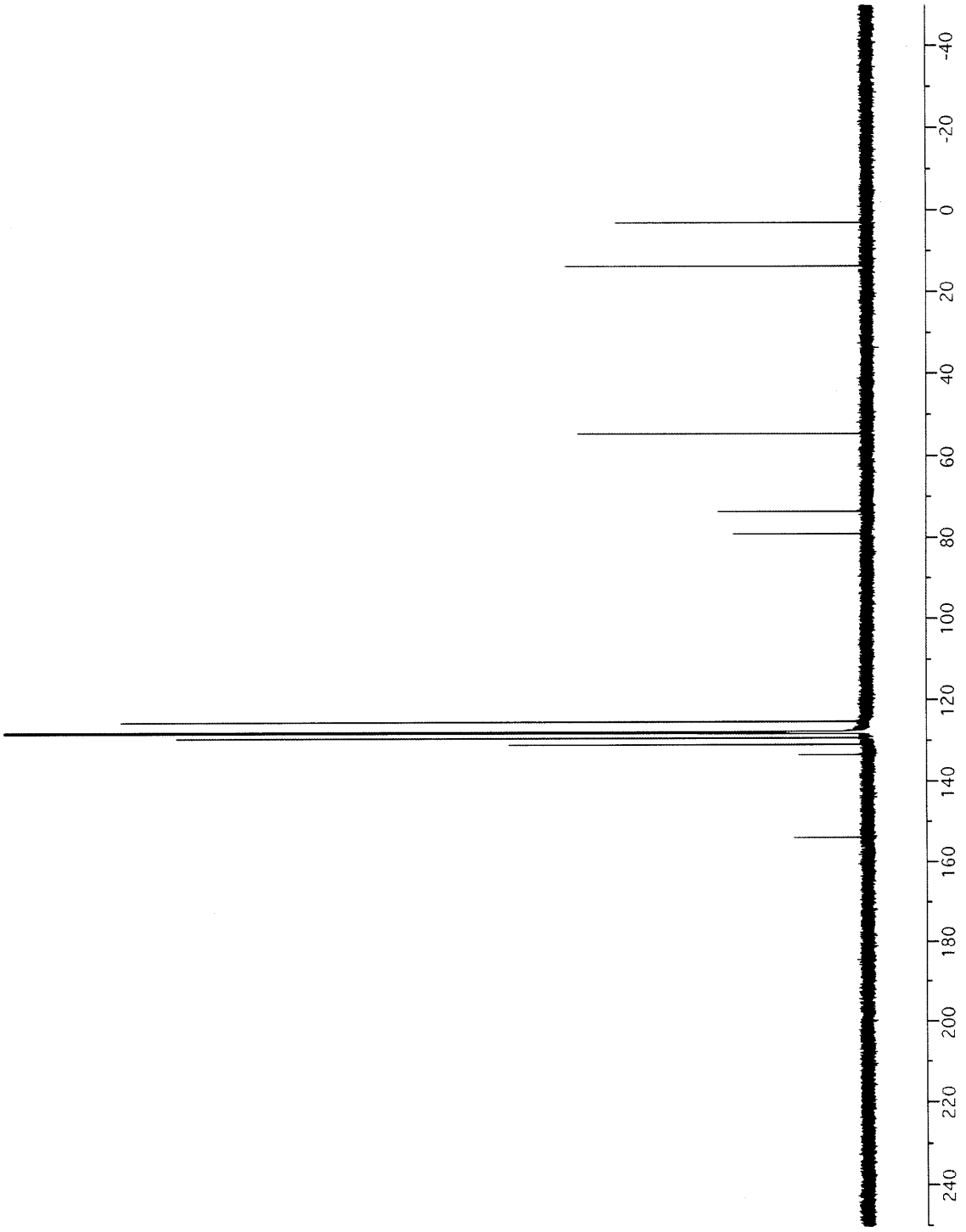

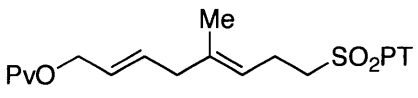

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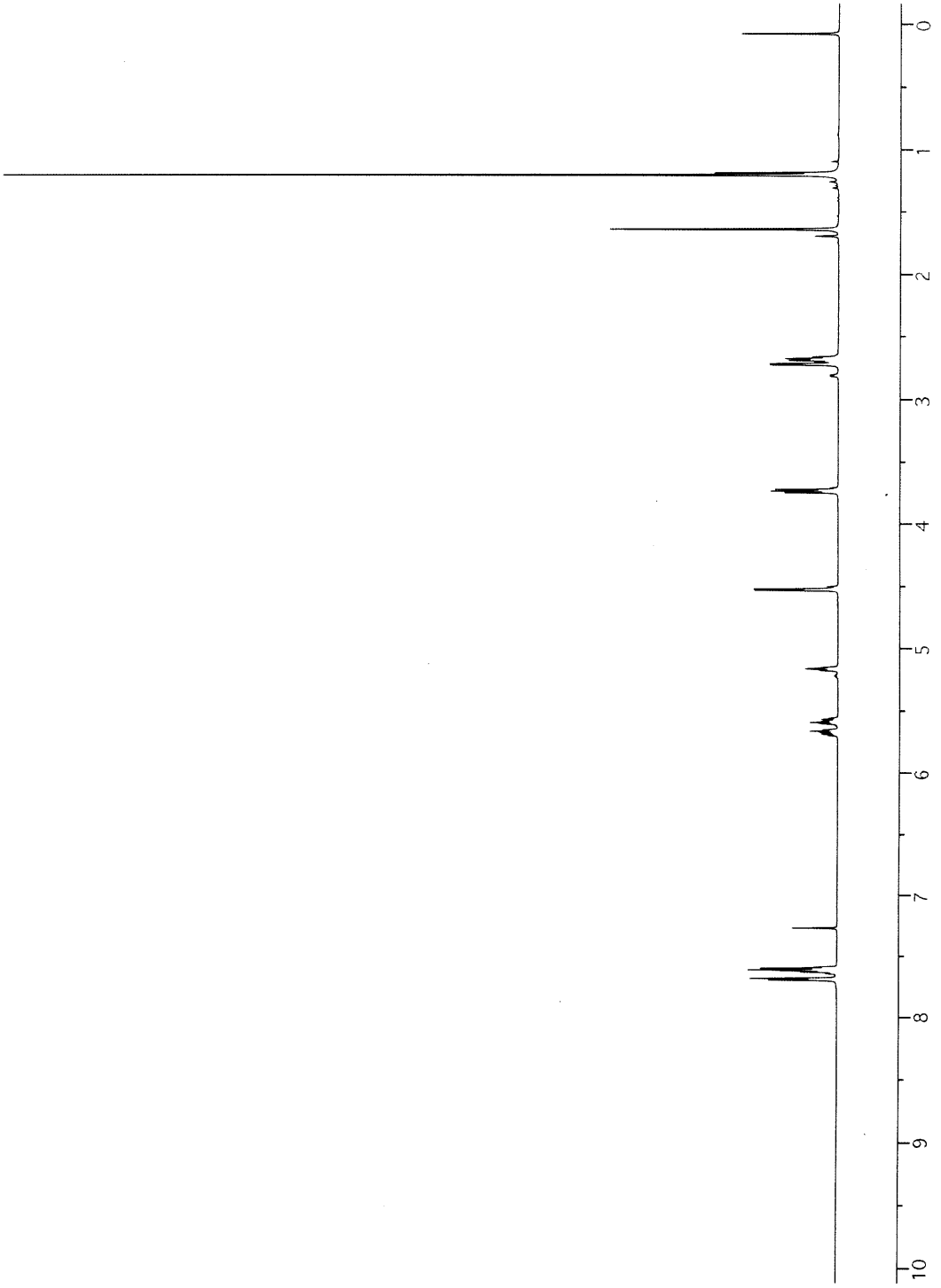

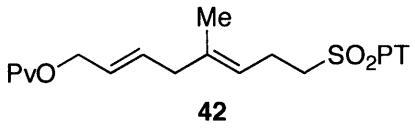

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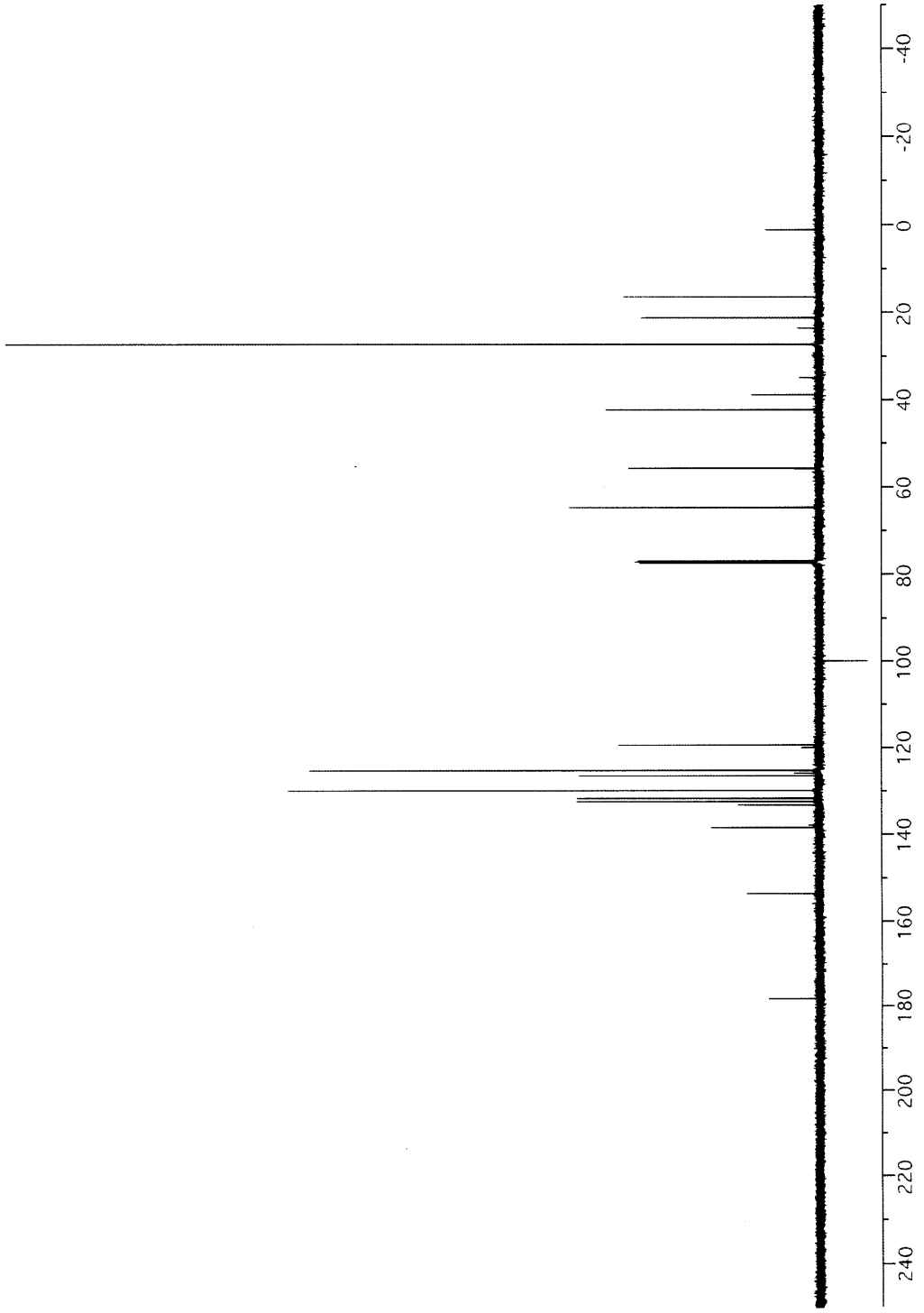

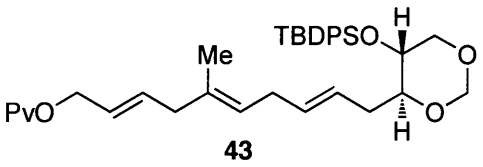

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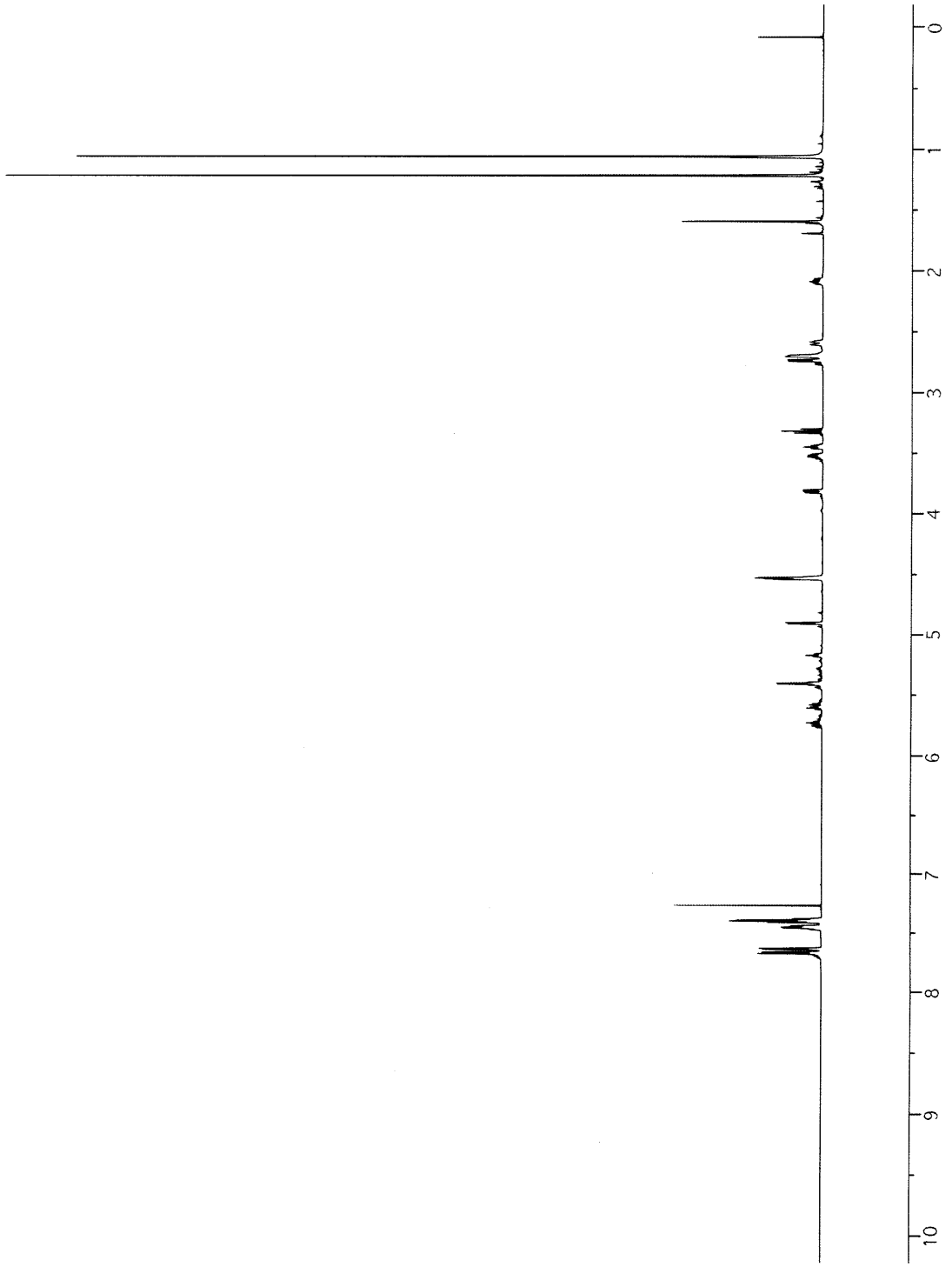

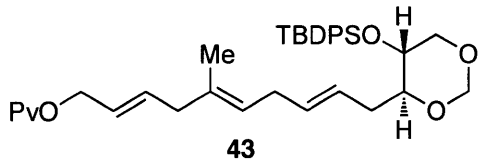

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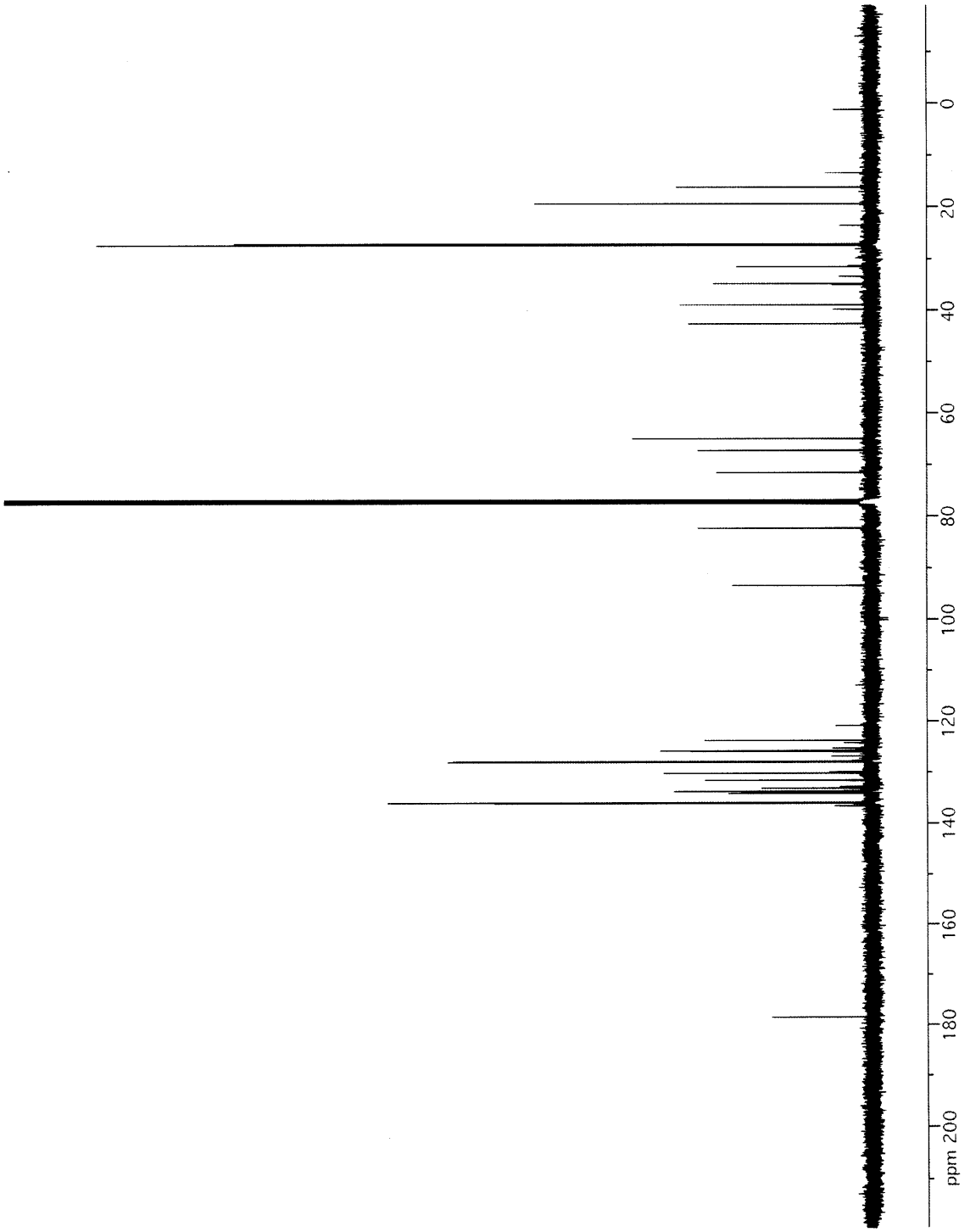

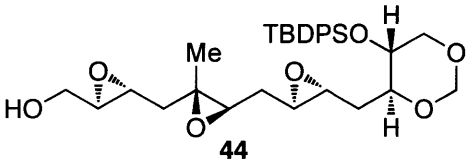

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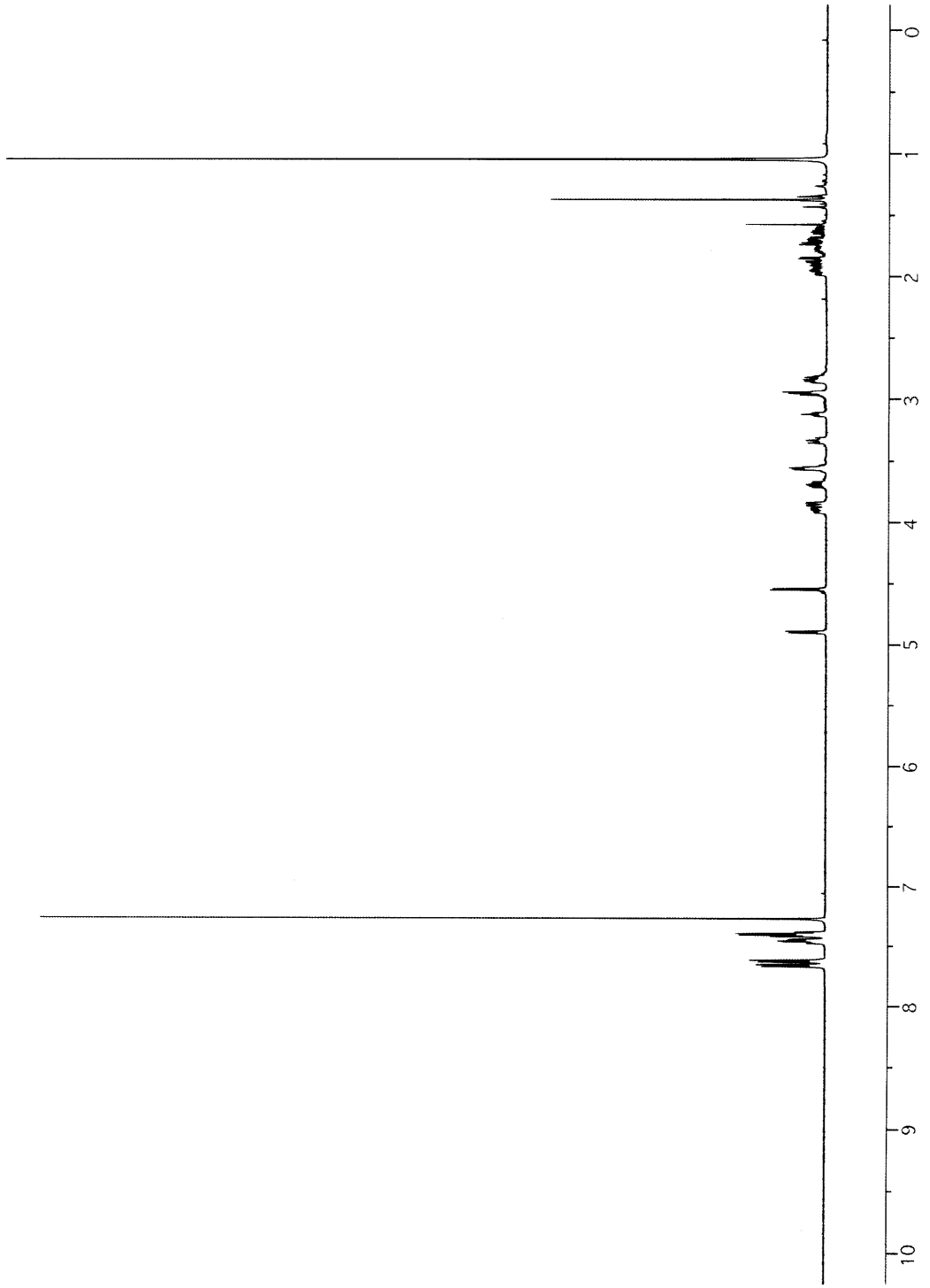

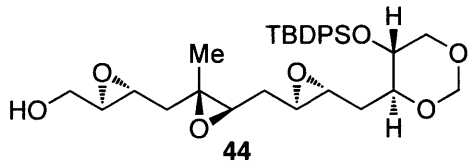
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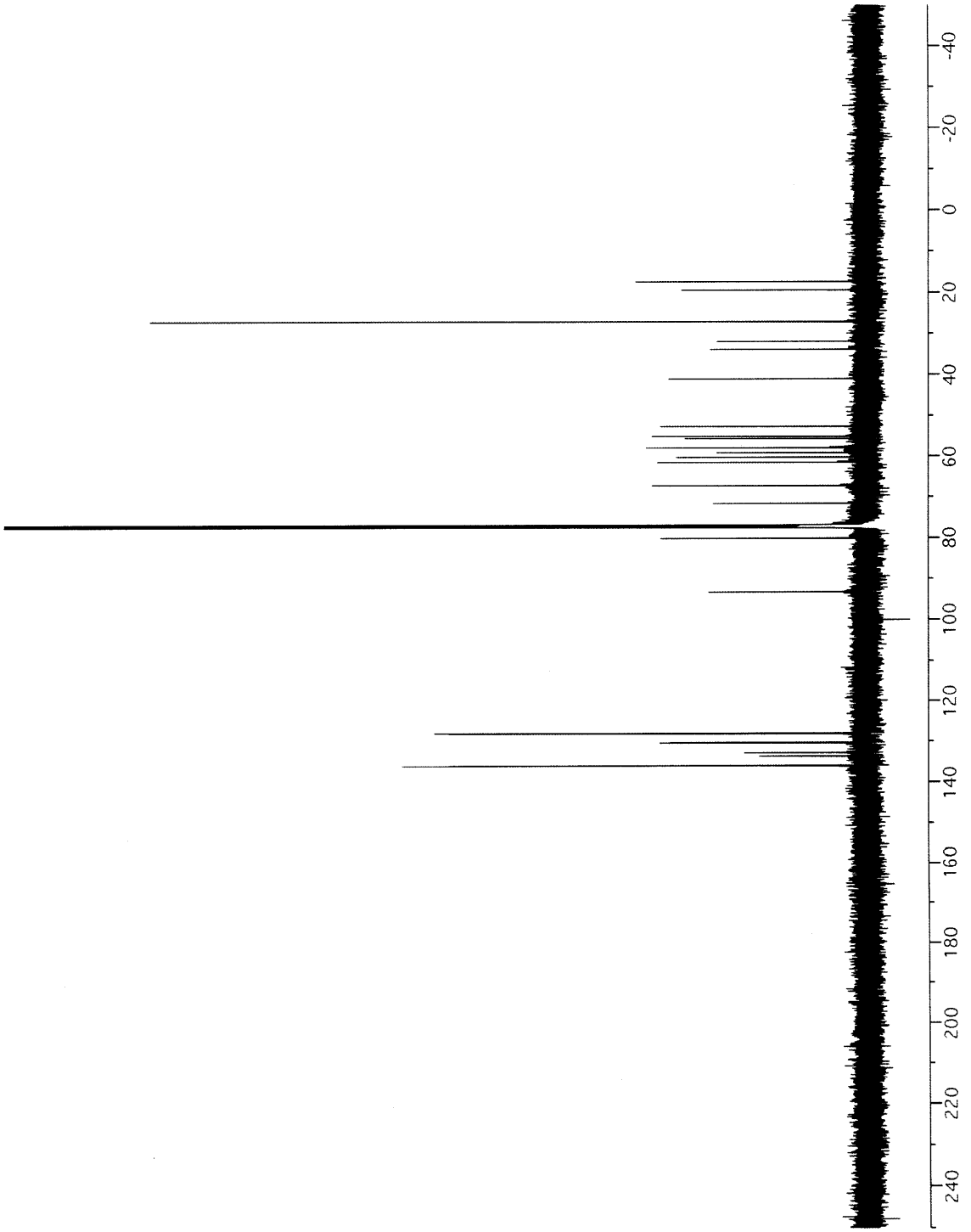
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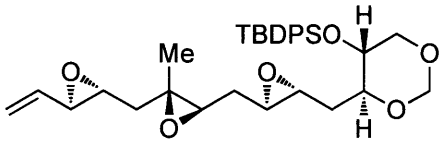

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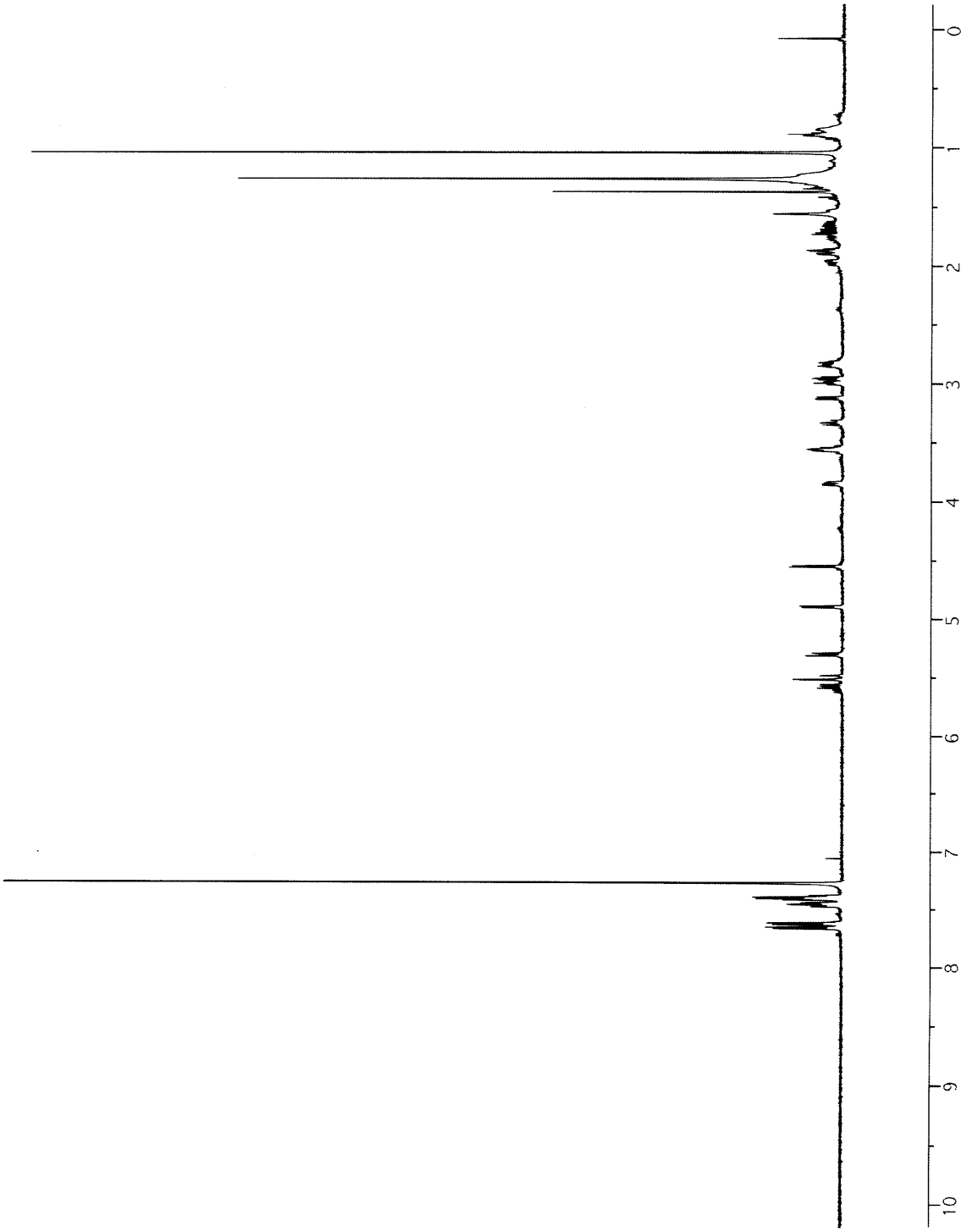

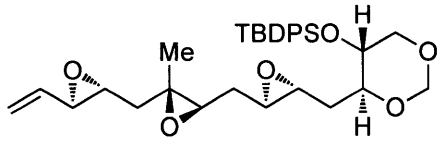
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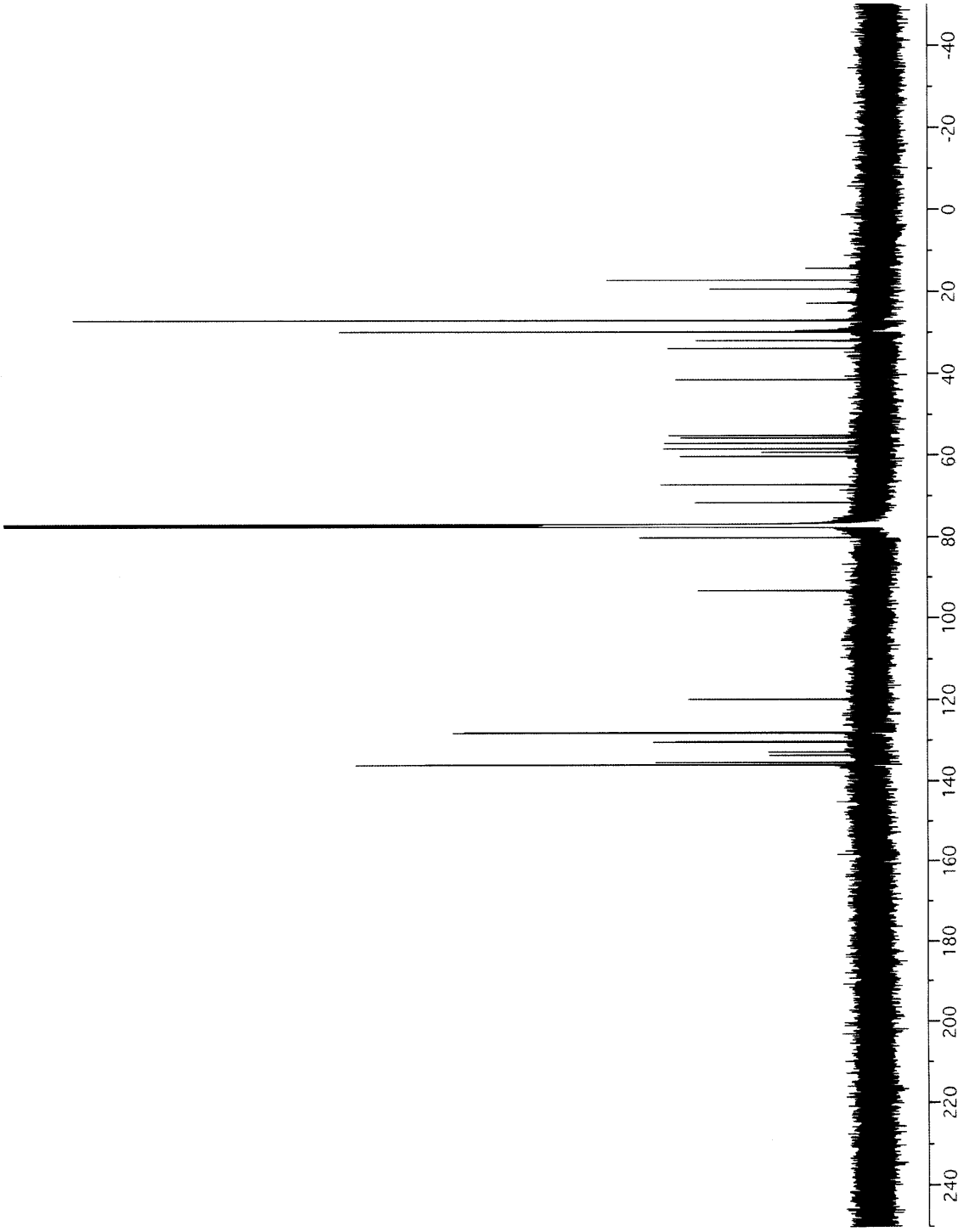
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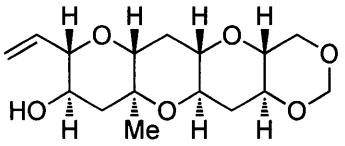

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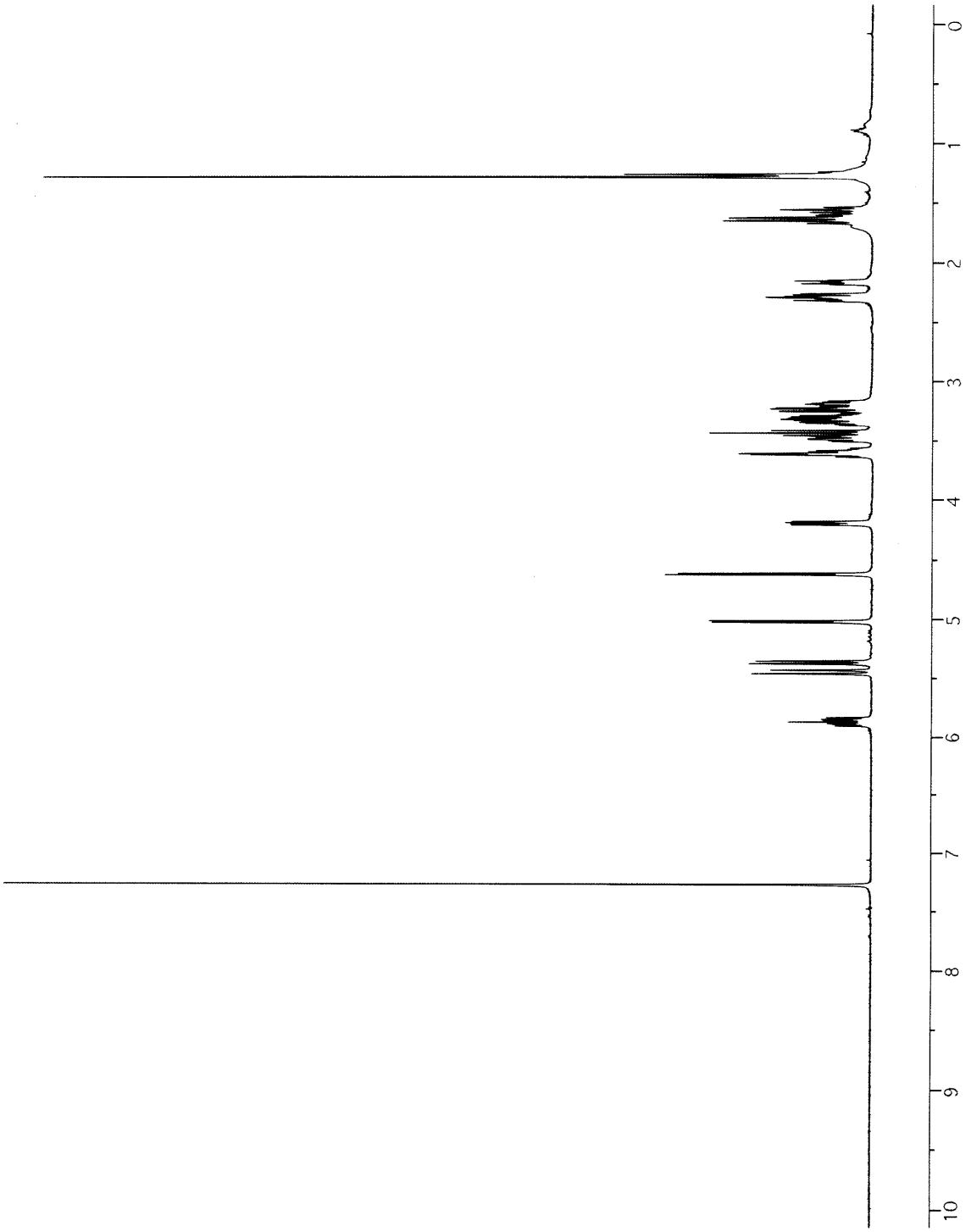

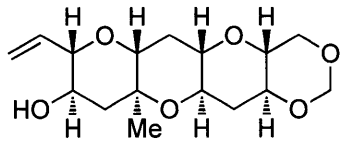
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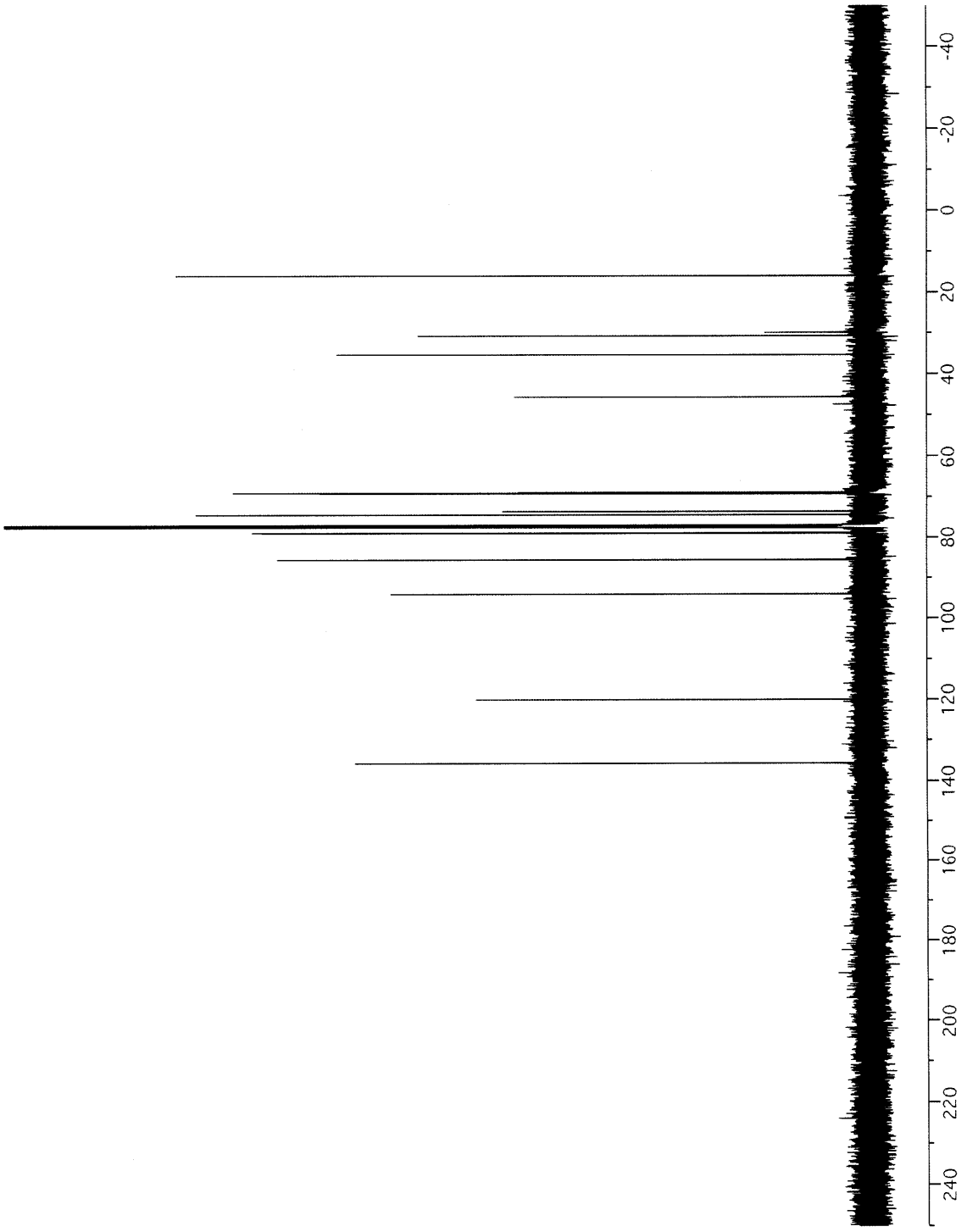
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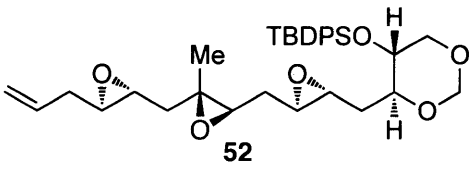

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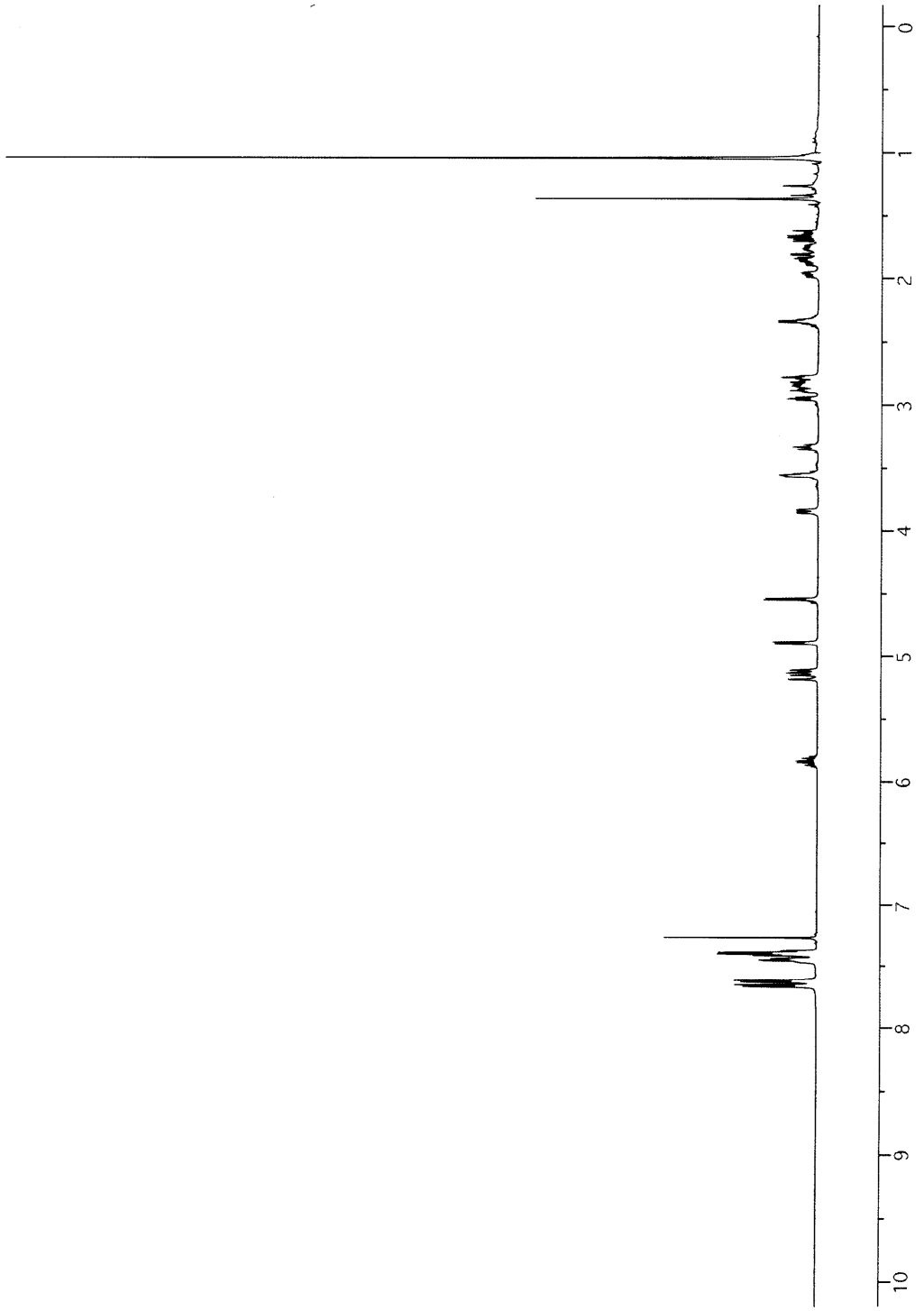

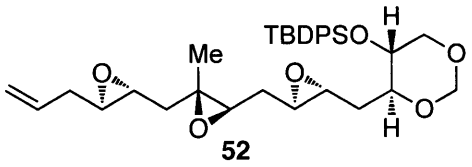
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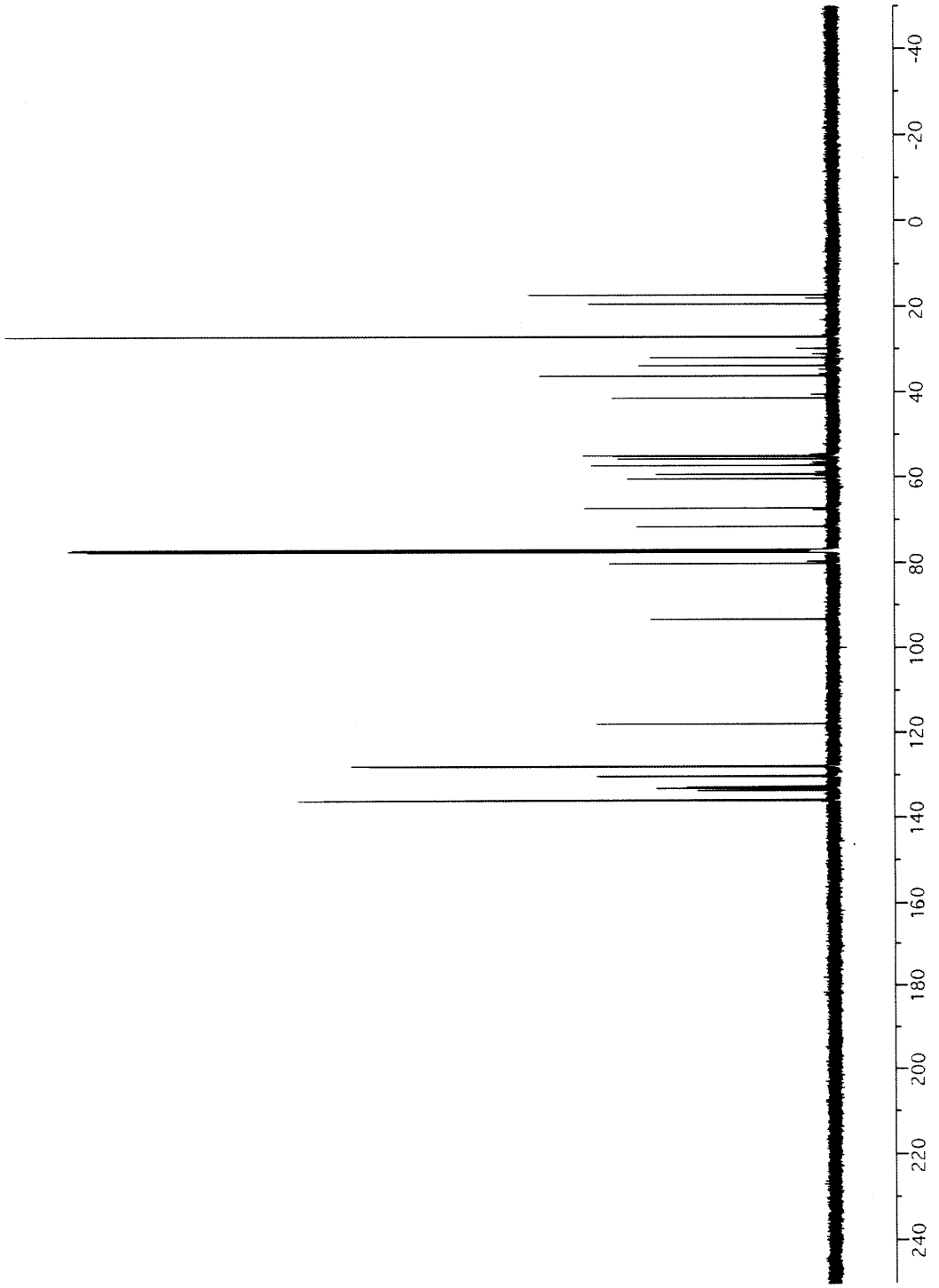
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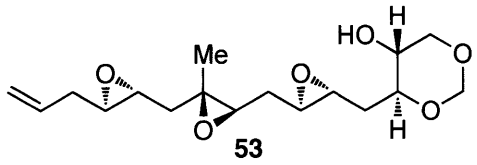

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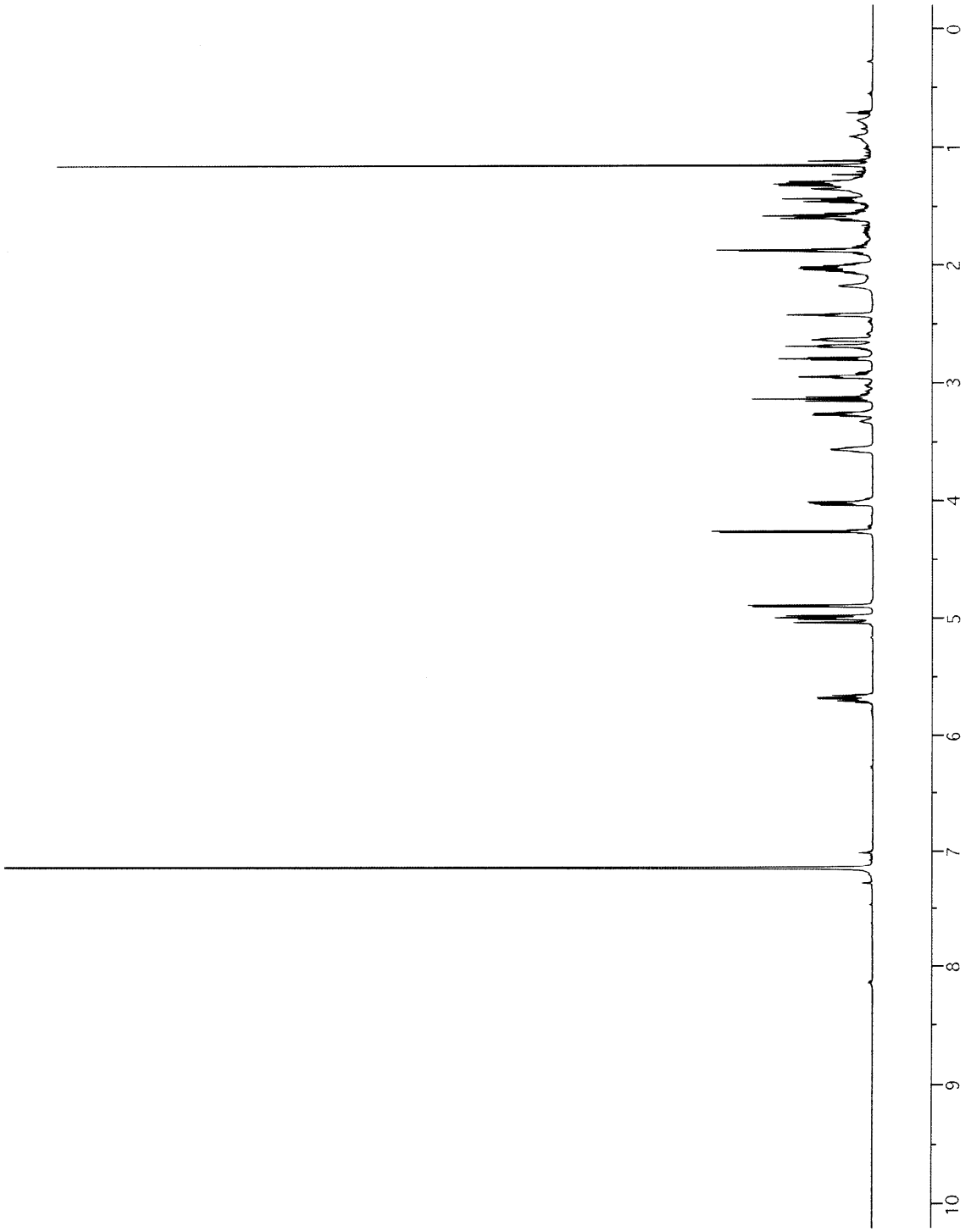

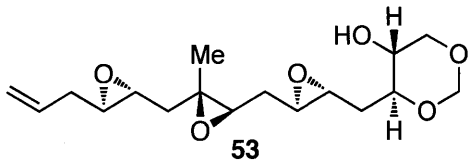

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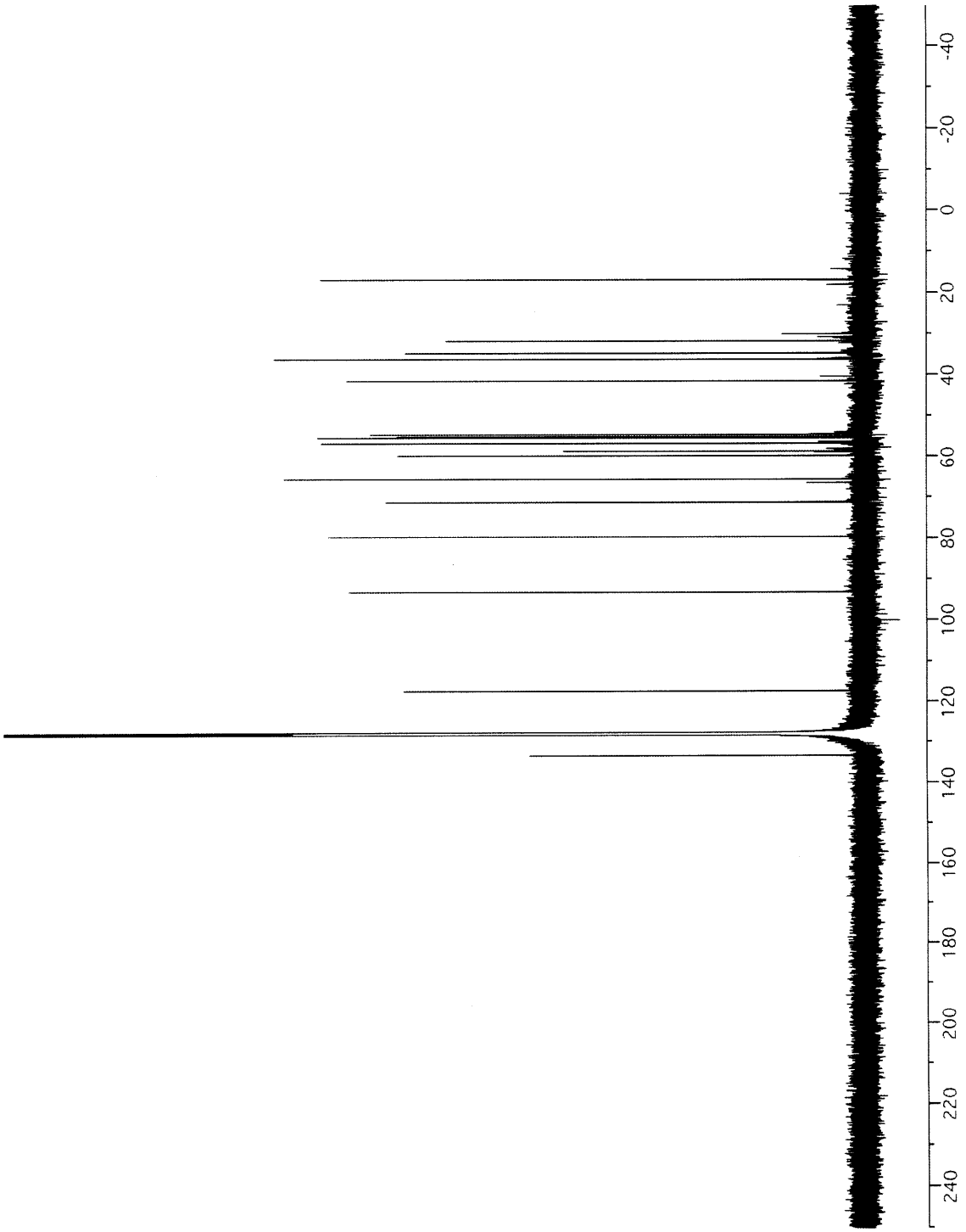

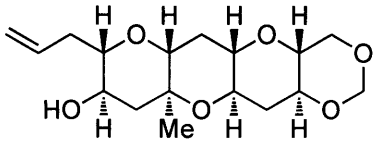

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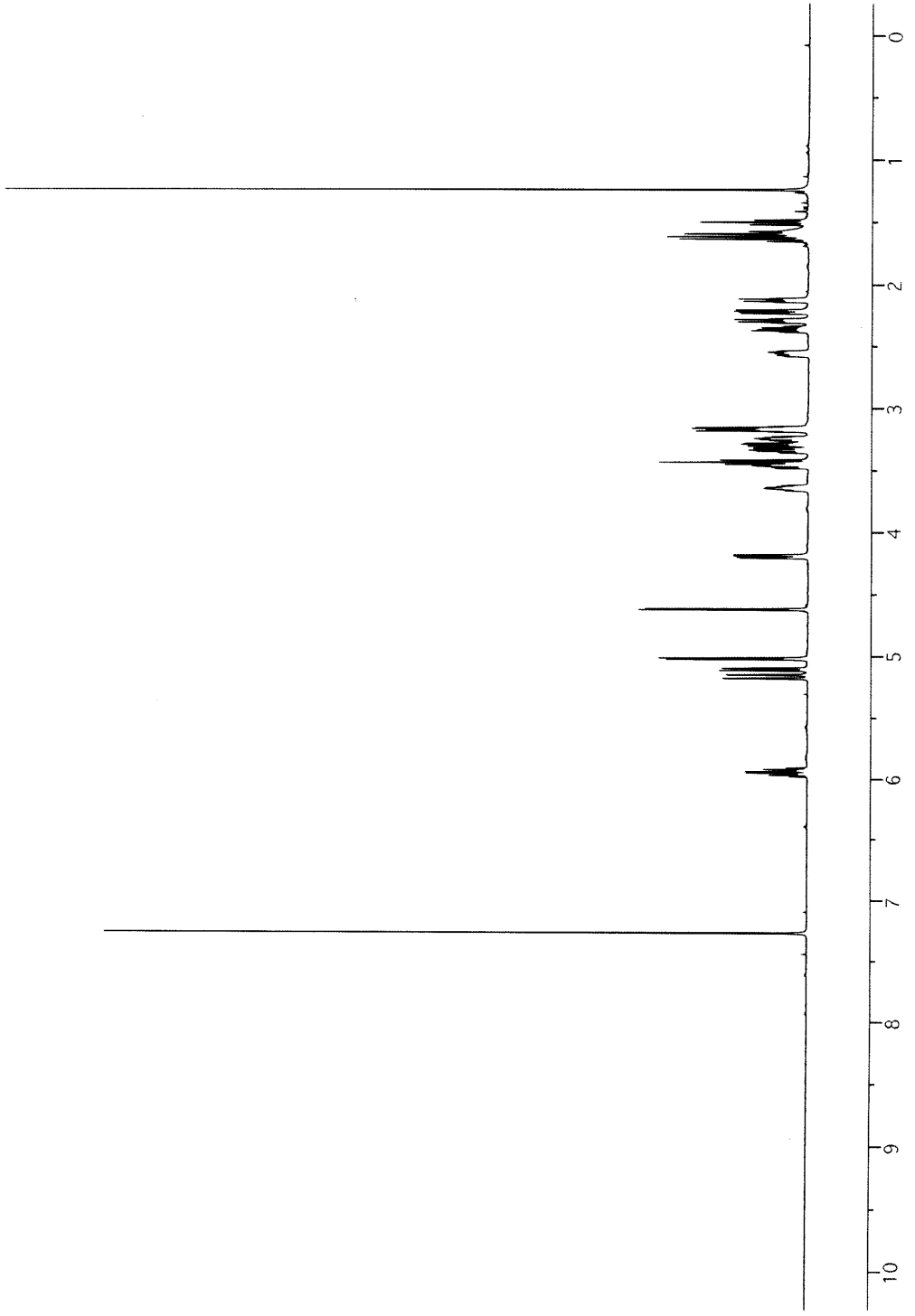

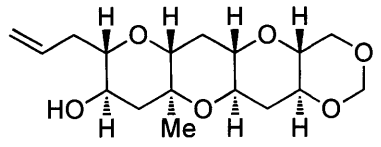
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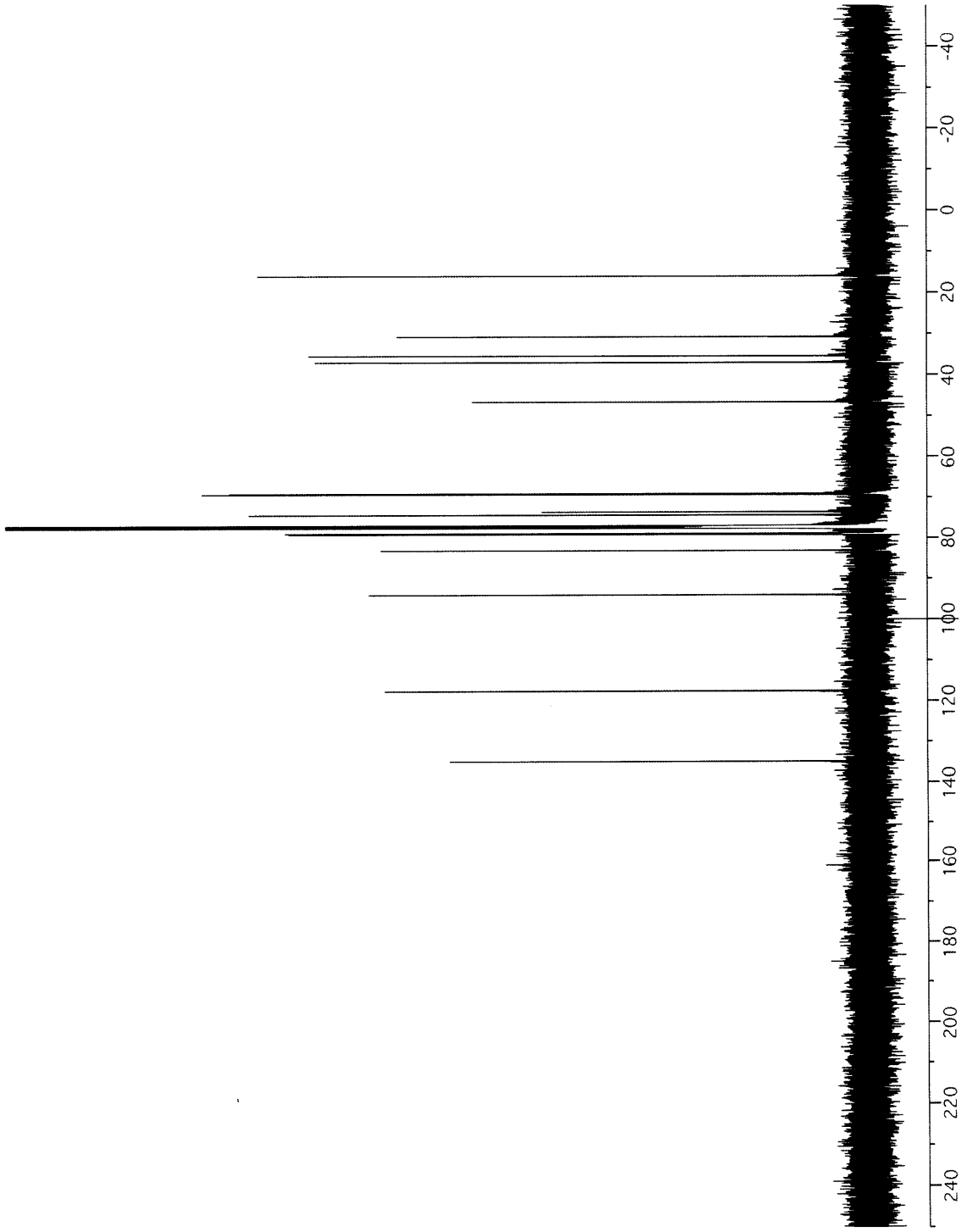
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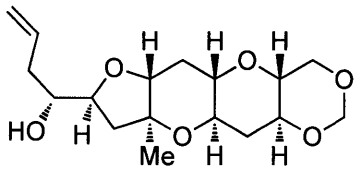

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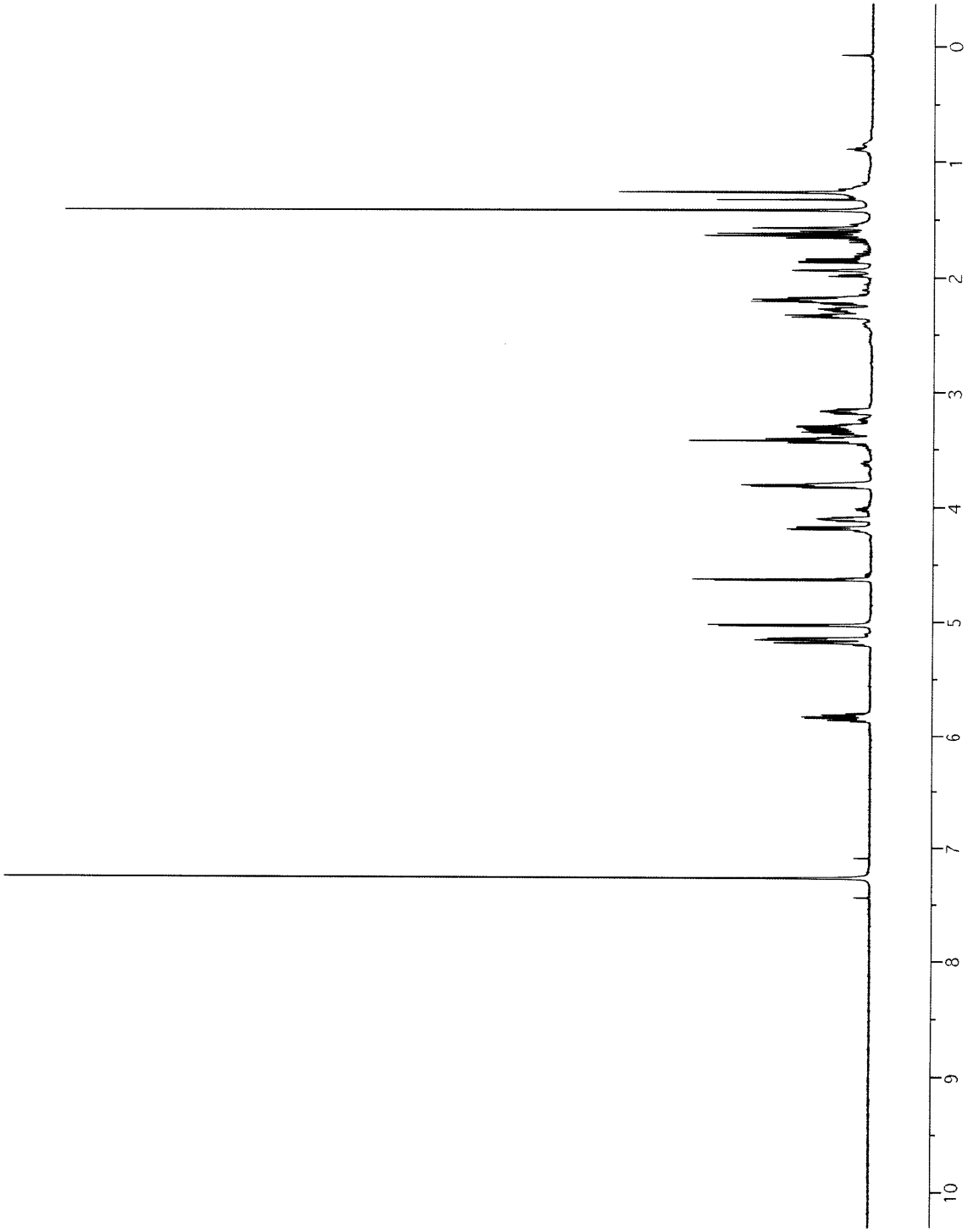

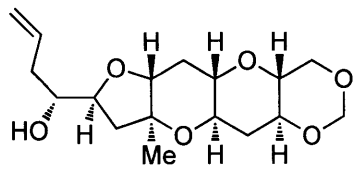
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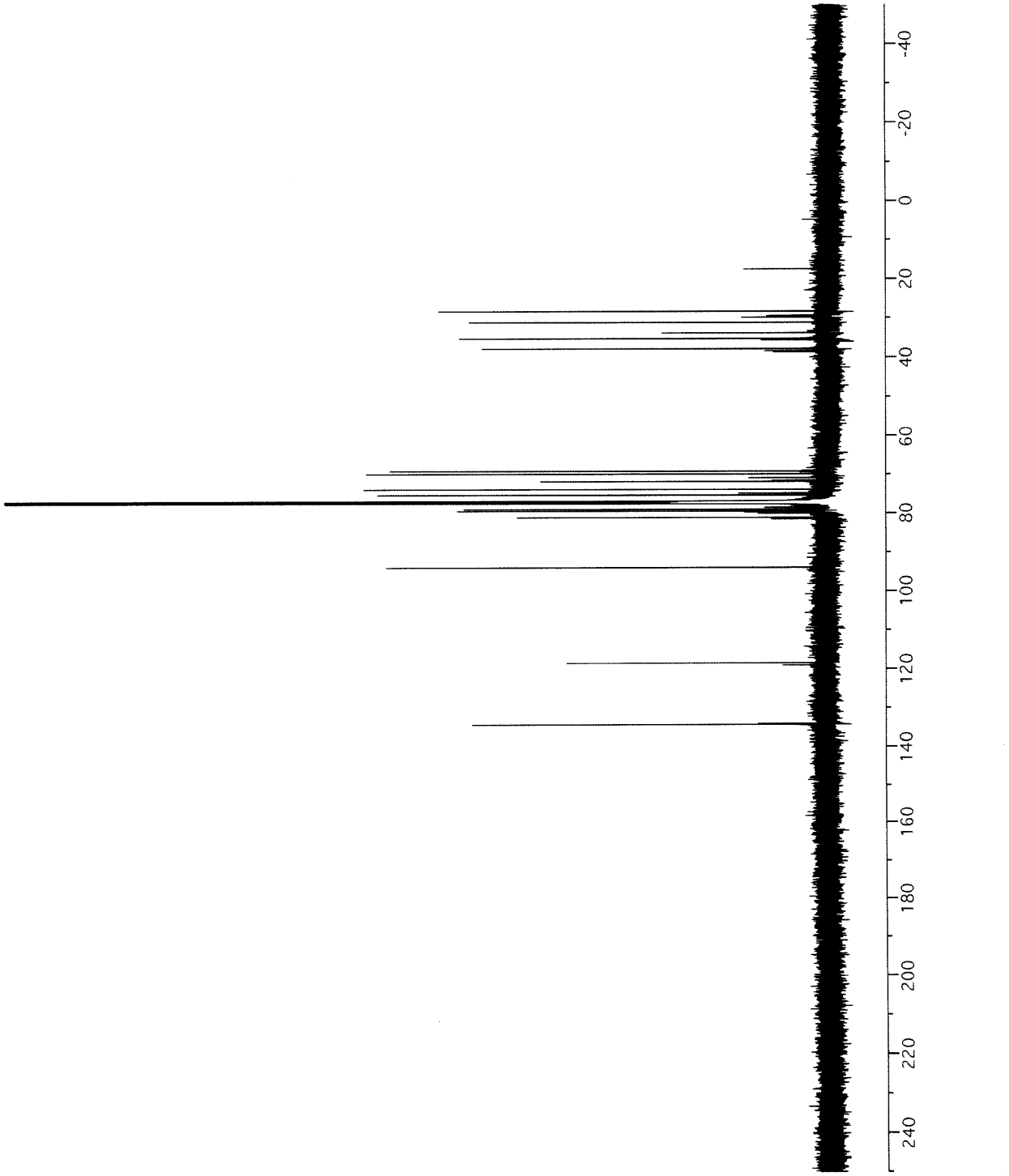
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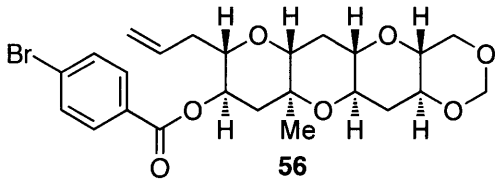

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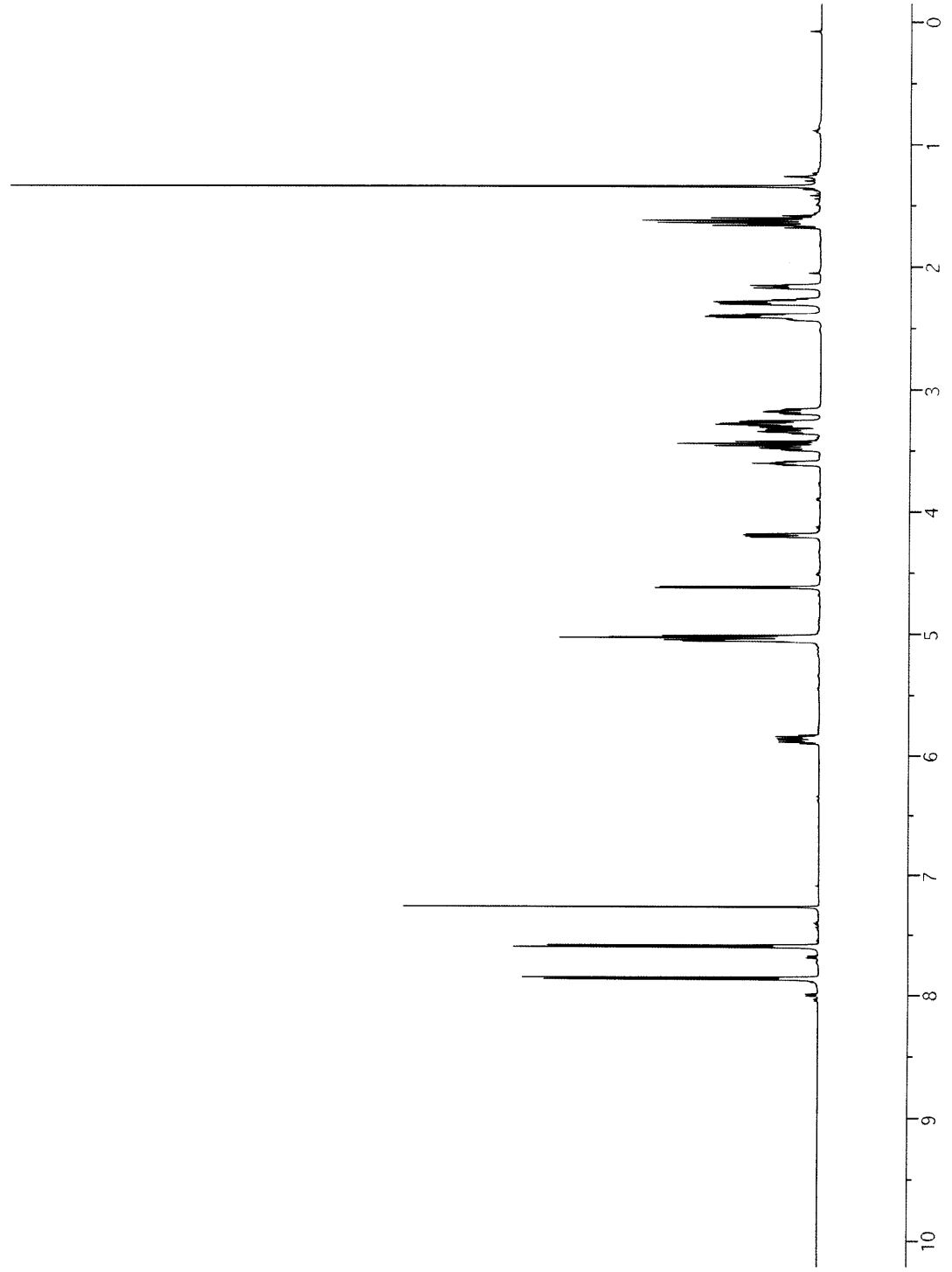

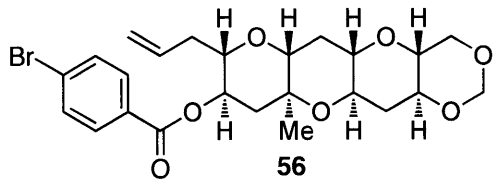

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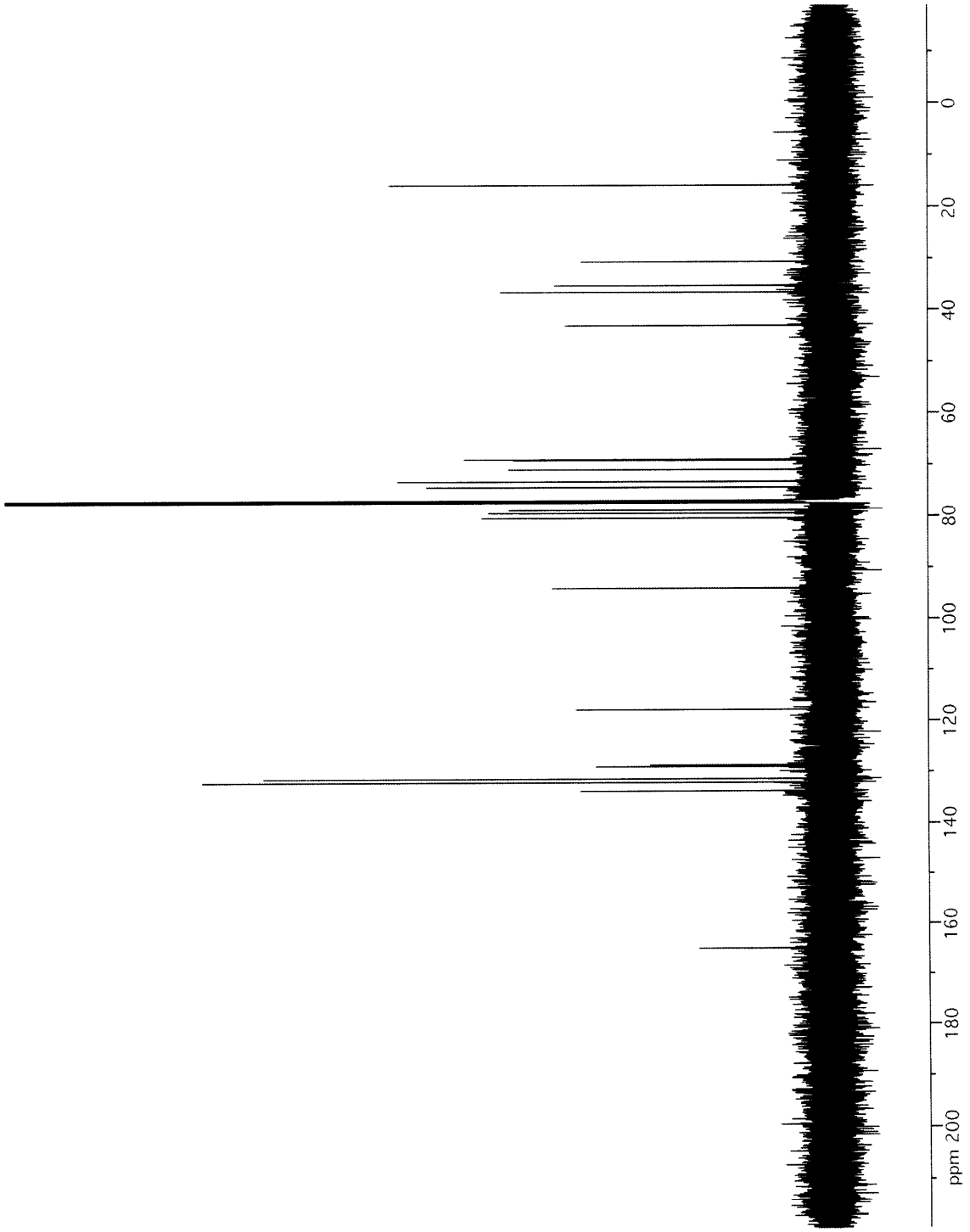

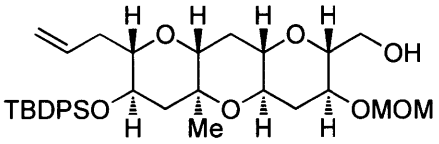

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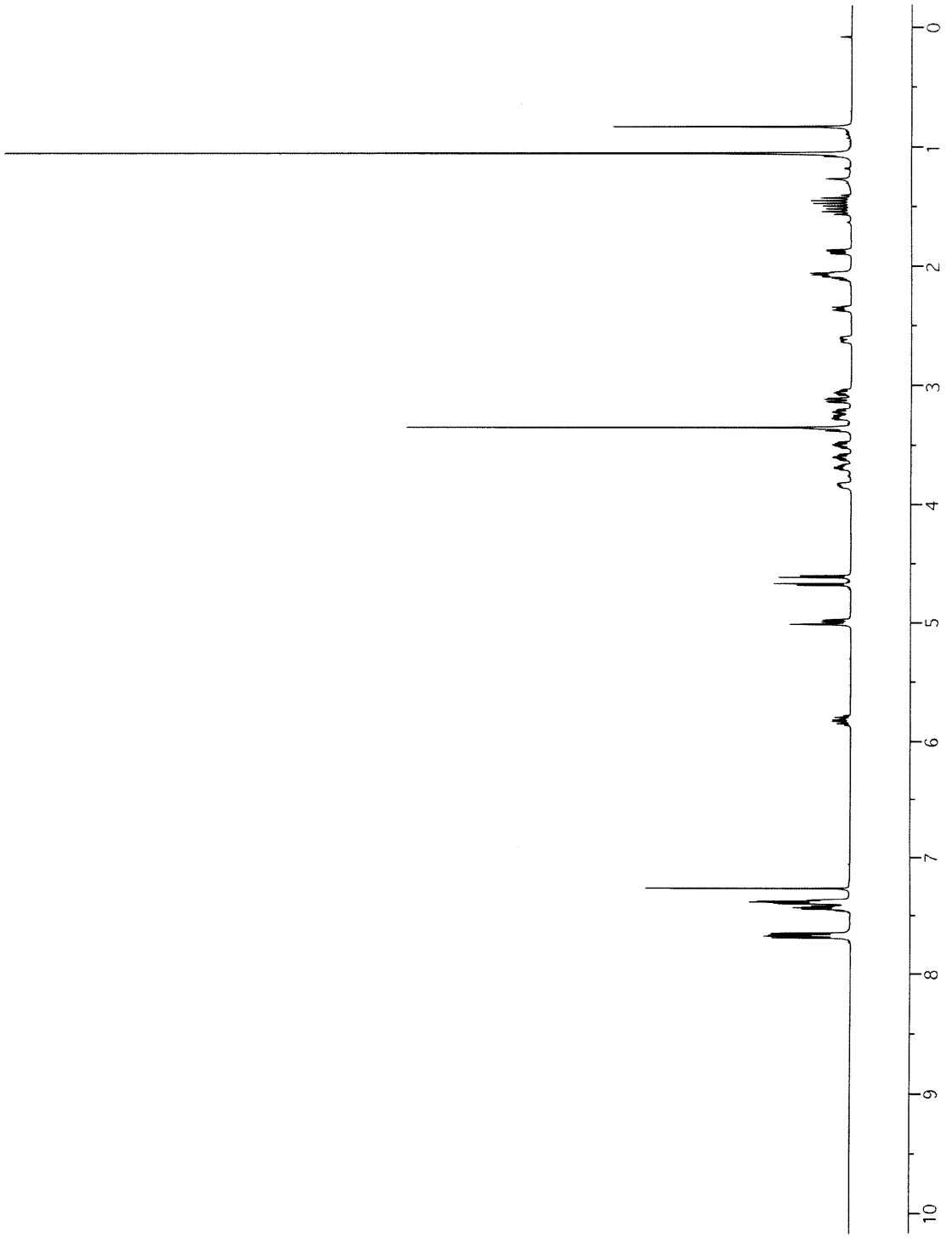

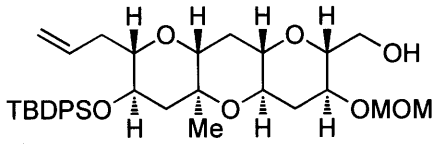
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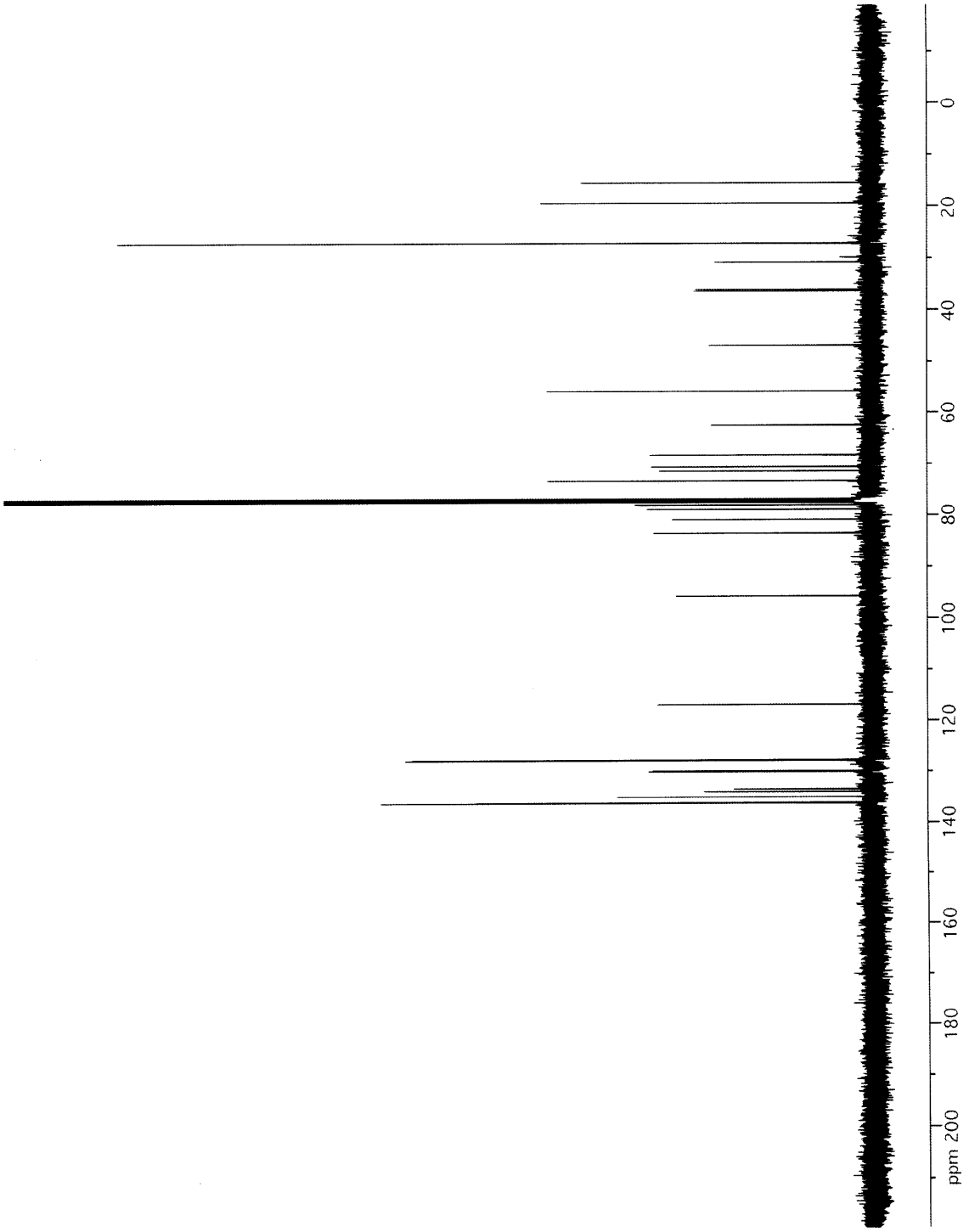
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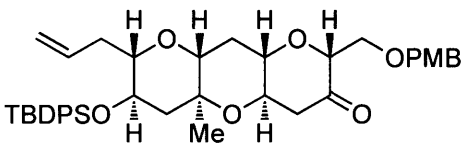

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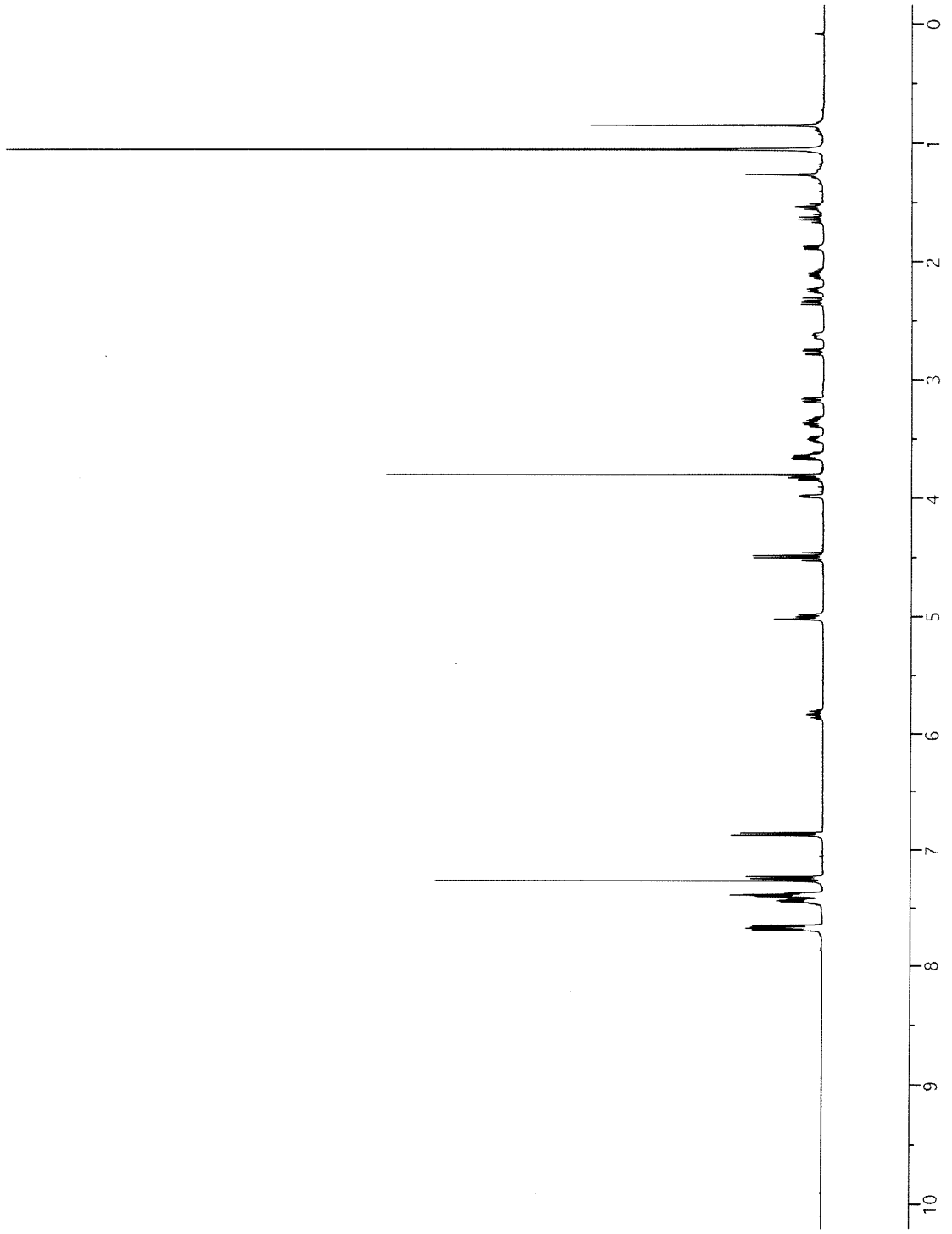

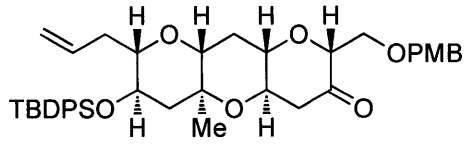
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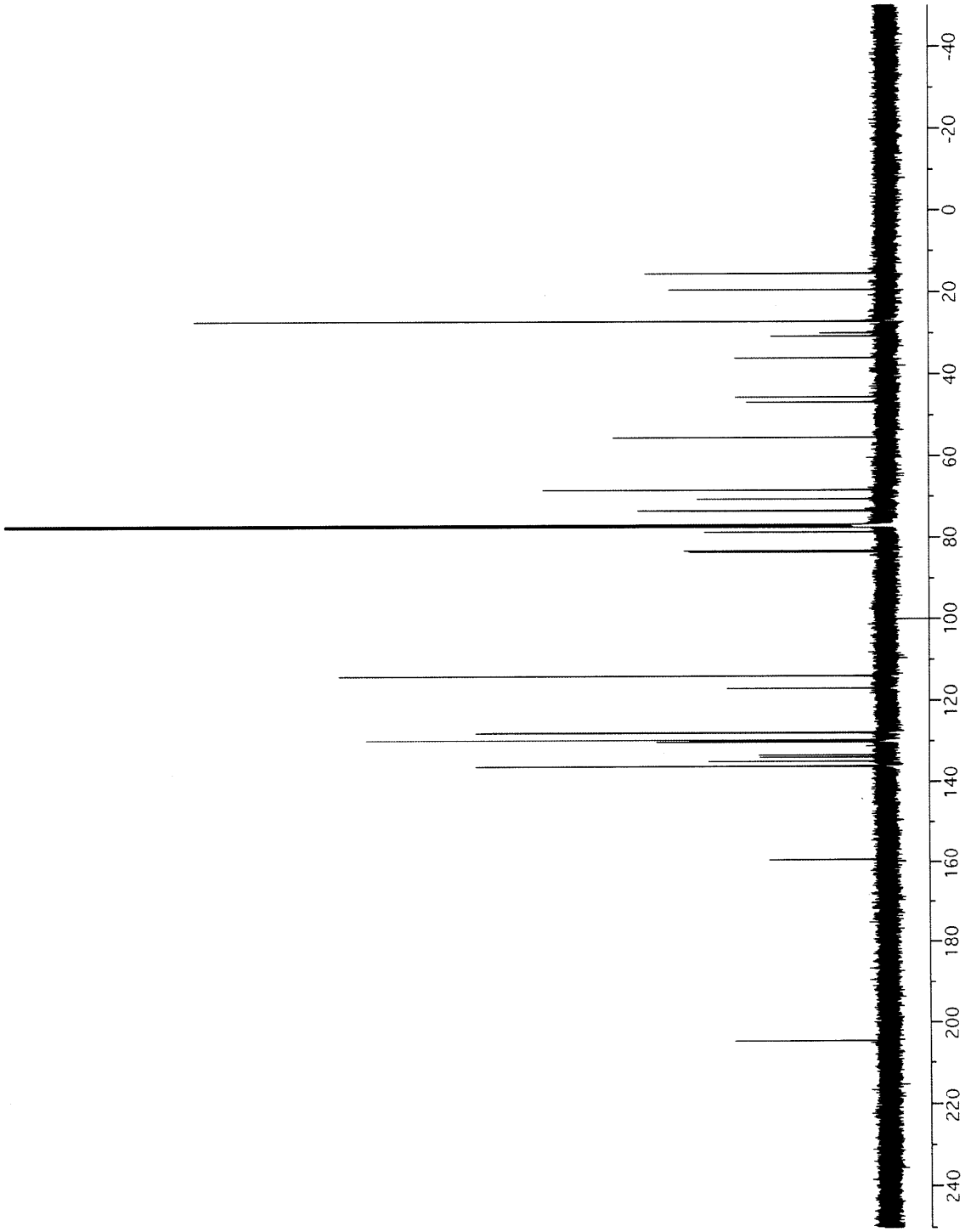
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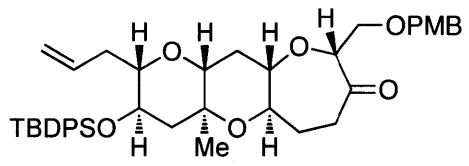

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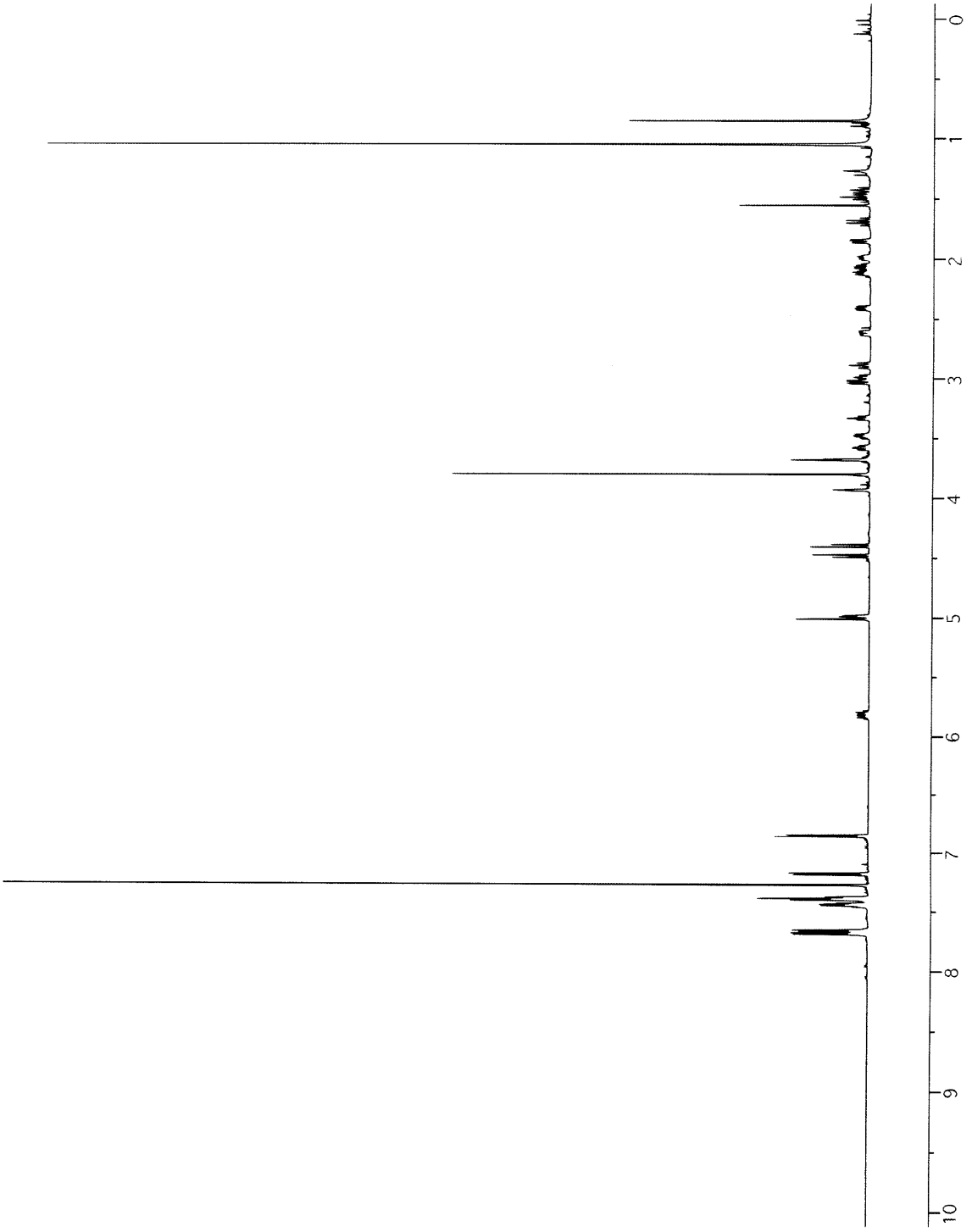

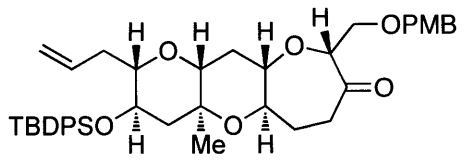
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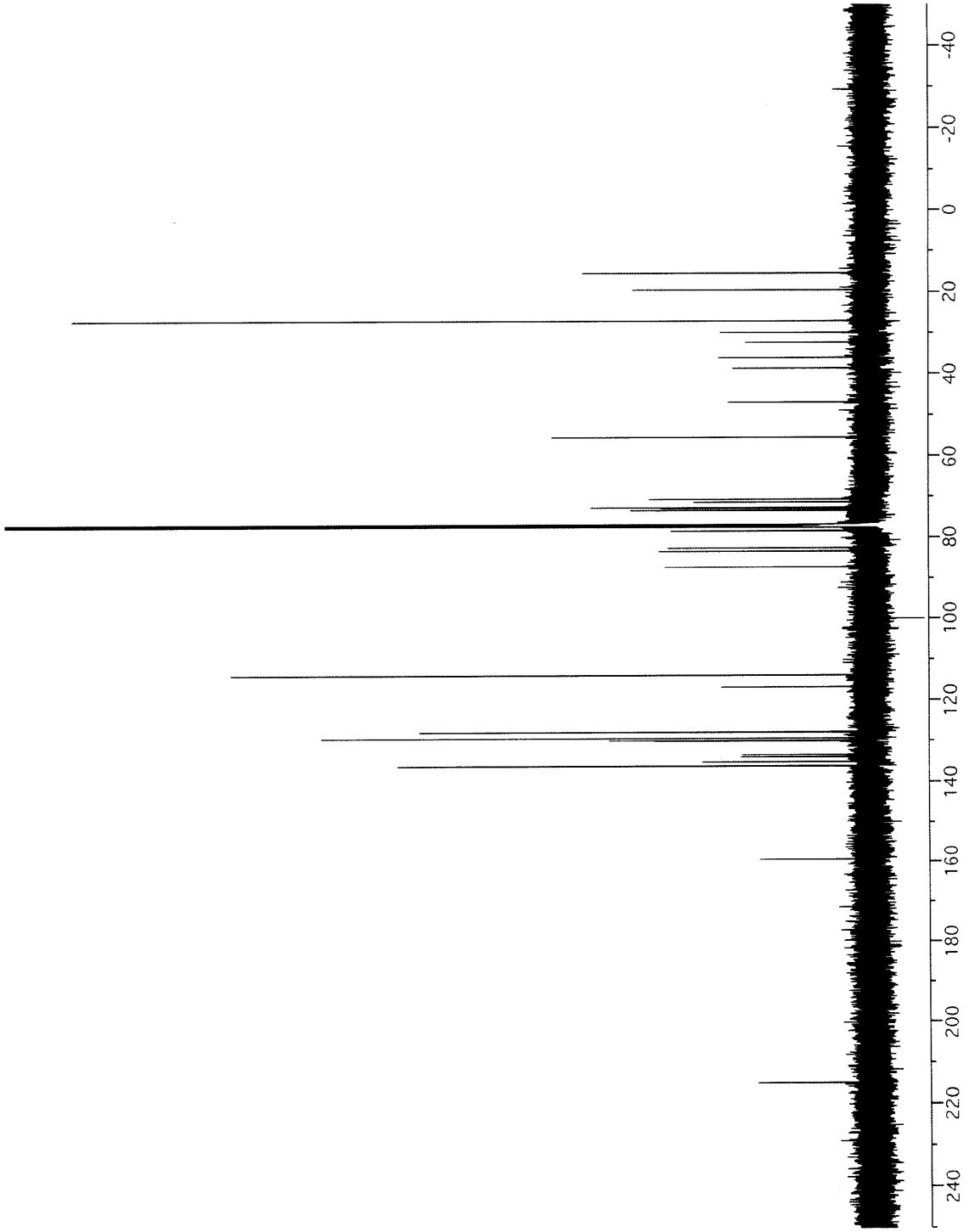
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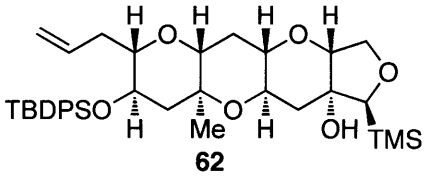

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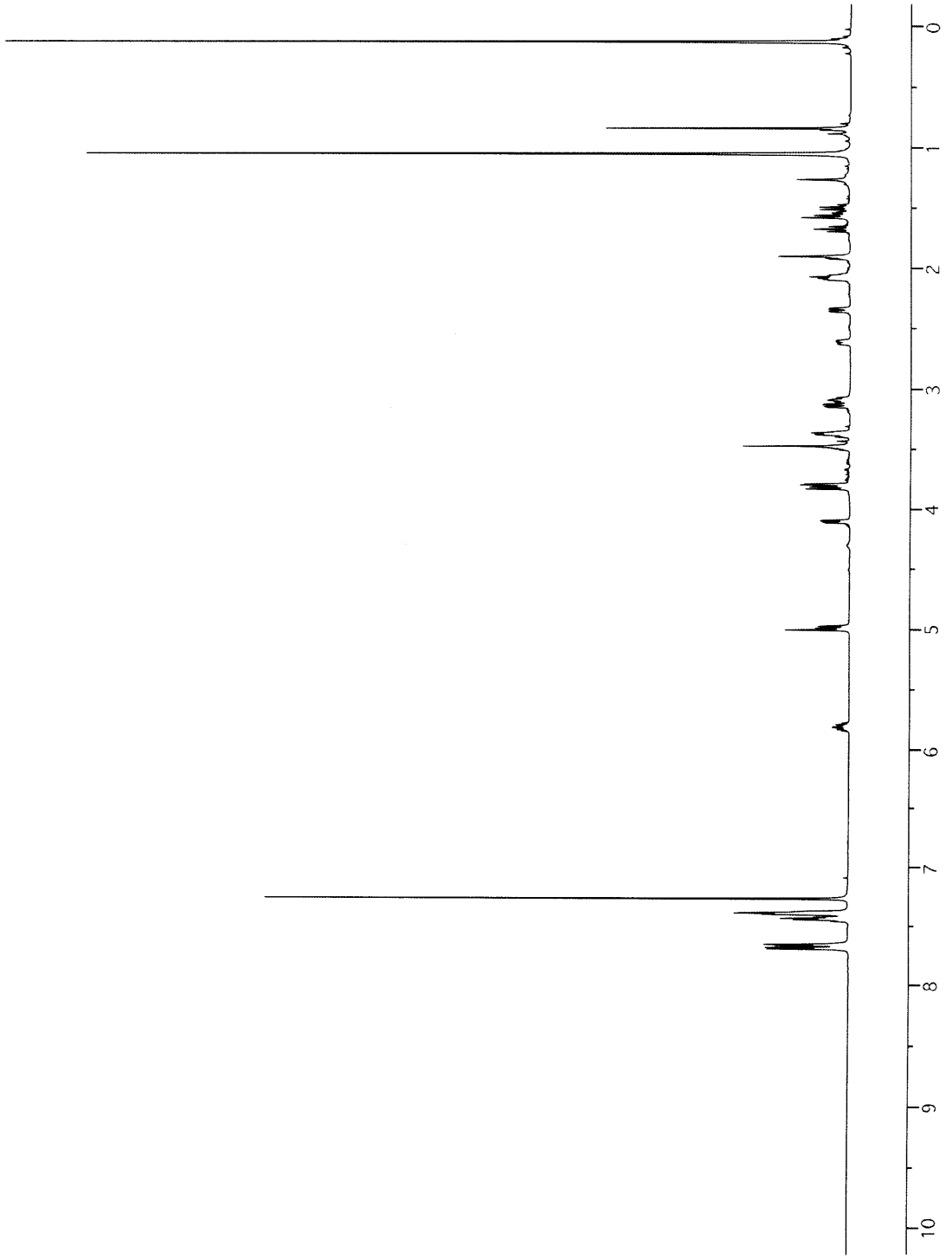

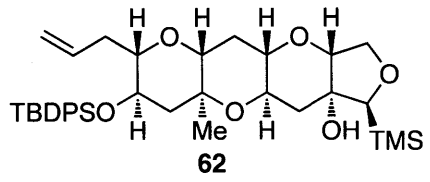
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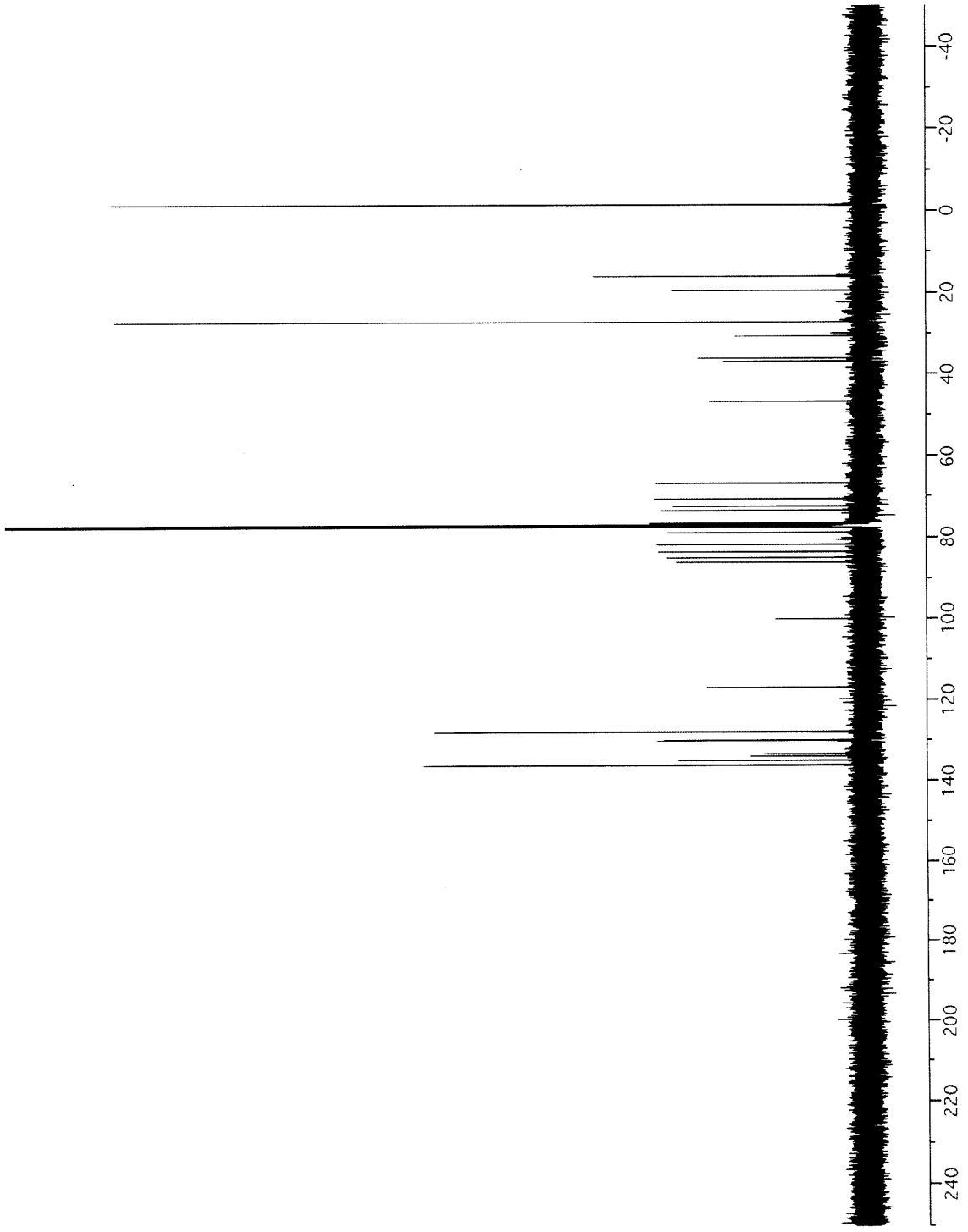
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Chapter VI

Conclusion: Potential Implications of the Foregoing Work on the Biosynthesis of the Ladder Polyethers.

Cascades of *endo*-selective epoxide-opening cyclizations promoted by water and templated by a preformed ring provide an efficient route to fused THP polycycles, subunits of the ladder polyether natural products.[1] From the earliest days of the Jamison group's interest in these molecules,[2] we have been inspired by the impressive cascades that conclude the proposed biosynthesis of the ladder polyethers.[3]

There are appealing parallels between *endo*-selective epoxide-opening cascades in water and the biosynthetic proposal, and it is therefore tempting to claim that reactions developed in the Jamison group may have some bearing on the biosynthetic puzzle. Indeed, there have been many cases in which organic synthesis has informed continuing biosynthetic investigation.[4] Two classes of natural products for which this is true, and which happen to have significant structural homology to the ladder polyethers, are the steroids and the polyether ionophores. In the case of the steroids, early suggestions of the biosynthesis of lanosterol from squalene (or a squalene-derived intermediate) via a cascade of cyclizations coalesced into the celebrated "Stork-Eschenmoser hypothesis."[5] Total syntheses of many steroids, including progesterone[6] and dihydrolanosterol,[7] mimicked this proposal and corroborated its viability. Ultimately, the Stork-Eschenmoser hypothesis was upheld on the basis of research in both organic chemistry and molecular biology. Similarly, in the case of the polyether ionophores, *in vitro* synthesis and biosynthetic inquiry progressed in concurrence and cooperation. For instance, the

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[1] *original reports:* (a) Vilotijevic, I.; Jamison, T. F. *Science*, **2007**, *317*, 1189. (b) Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6383. (c) Van Dyke, A. R.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 4430. (d) Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678. *account:* (e) Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, *38*, 3175.

[2] (a) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339. (b) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056. (c) Heffron, T. P.; Jamison, T. F. *Synlett* **2006**, 2329. (d) Heffron, T. P.; Simpson, G. L.; Merino, E.; Jamison, T. F. *J. Org. Chem.* **2010**, *75*, 2681.

[3] *original proposals:* (a) Nakanishi, K. *Toxicon* **1985**, *23*, 473. (b) Lee, M. S.; Qin, G.-w.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234. (c) Shimizu, Y. In *Natural Toxins: Animal, Plant, and Microbial*; Harris, J. B., Ed.; Clarendon: Oxford, 1986; p. 123. *recent review:* (d) Gallimore, A. R. *Nat. Prod. Rep.* **2009**, *26*, 266.

[4] For a personal perspective on this subject from E. E. van Tamelen, please see: van Tamelen, E. E. *Pure Appl. Chem.* **1981**, *53*, 1259.

[5] (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890. (c) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011. (d) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.

[6] (a) Johnson, W. S.; Gravestock, M. B.; McCarry, B. E.; *J. Am. Chem. Soc.* **1971**, *93*, 4332. (b) Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274. *account of this work and related cascades:* (c) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51.

[7] (a) van Tamelen, E. E.; Taylor, E. G.; Leiden, T. M.; Kreft, A. F. III *J. Am. Chem. Soc.* **1979**, *101*, 7423. *account of this work and related cascades:* Tamelen, E. E. *Acc. Chem. Res.* **1974**, *8*, 152.

realization of efficient, highly *exo*-selective cascades of epoxide-opening cyclization for the synthesis of chains of tethered THF rings[8] provided evidence for the Cane-Celmer-Westley hypothesis for the biosynthesis of monensin,[9] which was later confirmed via gene sequencing[10] and isolation of a biosynthetic intermediate.[3d,11]

Thus it is highly tempting to construe the success of templated, water-promoted, *endo*-selective epoxide-opening cascades as "proof" of the existence of such cascades in the biogenesis of the ladder polyethers. However, we remind the reader that there is no direct evidence that epoxide-opening cyclization is involved at any point in the biosynthesis.[12] Furthermore, there are a number of serious inconsistencies that make it extremely unlikely that the ladder polyethers are derived from "true" water-promoted epoxide-opening cascades, in the absence of enzymatic mediation. Among the most important are the following:

1. The rate of water-promoted epoxide-opening is impractically slow. At ambient temperature, cascades of only three epoxides take months to finish. A full-blown water-promoted cascade of 10 or 14 cyclizations to produce a ladder polyether of the scale of brevetoxin B or gymnocin B would require a reaction time many times longer. High temperatures (60 or 70 °C) are required to shorten reaction times for cascades of two or three epoxides to hours or days, and these temperatures are inconsistent with the environmental conditions inhabited by producing dinoflagellates.
2. Such ambitious cascades to a full ladder polyether natural product remain completely implausible at the moment, as we have not achieved water-promoted *endo*-selective epoxide opening to form seven- or eight-membered rings, nor have

---

[8] *original reports:* (a) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312. (b) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106. (c) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105. *review:* (d) Vilotijevic, I.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 5250.

[9] Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.

[10] Leadlay, P. F.; Staunton, J.; Oliynyk, M.; Bisang, C.; Cortés, J.; Frost, E.; Hughes-Thomas, Z. A.; Jones, M. A.; Kendrew, S. G.; Lester, J. B.; Long, P. F.; McArthur, H. A. I.; McCormick, E. L.; Oliynyk, Z.; Stark, C. B. W.; Wilkinson, C. J. *J. Ind. Microbiol. Biotech.*, **2001**, *27*, 360.

[11] Bhatt, A.; Stark, C. B. W.; Harvey, B. M.; Gallimore, A. R.; Demydchuk, Y. A.; Spencer, J. B.; Staunton, J.; Leadlay, P. F. *Angew. Chem. Int. Ed.*, **2005**, *44*, 7075.

[12] Please see the introductory Chapter I for a more thorough discussion of what is and is not known about the biosynthesis of the ladder polyethers.

we been able to use medium rings as templates for six-membered ring formation.[13]

3. Even in cascades to form fused THP polycycles, water-promoted epoxide-opening cascades may not be sufficiently efficient to constitute a viable biosynthetic route. While yields in cascades of all *trans*-disubstituted epoxides are quite high yielding (averaging about 85% yield per THP formation),[1a] yields decline markedly upon appendage of methyl substituents to the epoxide (see Chapter II).

We therefore believe, as we have previously remarked,[1a] that water is best viewed as an interesting surrogate and mimic of enzymatic activation, rather than as a genuine candidate for promoter in the biosynthesis of the ladder polyethers. The conformational constraints established by the template, which alter the trajectory of approach of hydroxyl nucleophile to epoxide electrophile, may be viewed as a proxy for those imposed by the active site of an epoxide hydrolase enzyme. The primary role of water as promoter seems to be as hydrogen bond donor, to activate the epoxide electrophile, and as proton shuttle. In its capacity as epoxide activator it appears to act similarly to the two activating tyrosine residues of limonene-1,2-epoxide hydrolase[14] and other, structurally alike hydrolases believed to catalyze cyclization in polyether ionophore biosynthesis.[3d,15]

We therefore posit that if epoxide-opening cyclizations do occur in the biogenesis of the ladder polyethers, enzymatic mediation is essential. That said, our group's investigations of epoxide-opening cascades in water may have some relevance to the biosynthesis of the ladder polyethers. We are particularly preoccupied with the problem of methyl (Me) substitution, which was the focus of Chapter II. As mentioned previously, the incorporation of Me substituents on epoxides in a cascade substrate leads to lower

---

[13] Byers, J. A.; Vilotijevic, I.; Jamison, T. F. *Manuscript in preparation.*

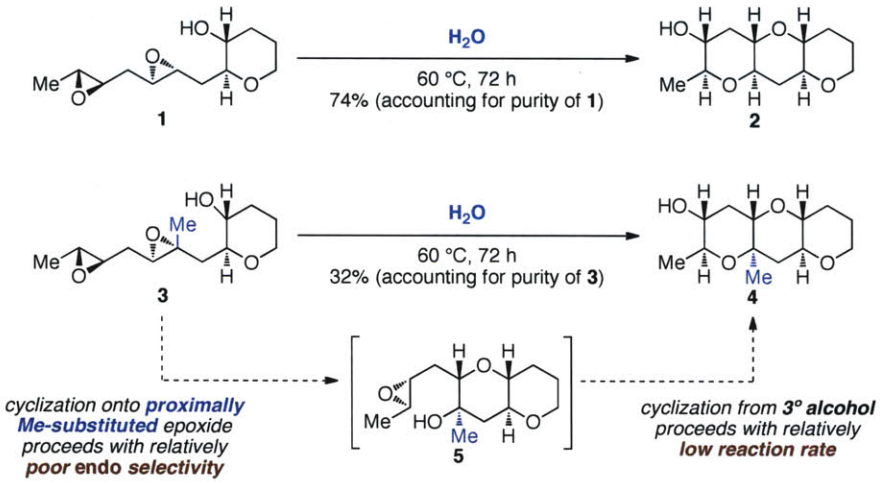
[14] (a) van der Werf, M. J.; Overkamp, K. M.; de Bont, J. A. M. *J. Bacteriol.* **1998**, *180*, 5052. (b) Arand, M.; Hallberg, B. M.; Zou, J.; Bergfors, T.; Oesch, F.; van der Werf, M. J.; de Bont, J. A. M.; Jones, T. A.; Mowbray, S. L. *EMBO J.* **2003**, *22*, 2583.

[15] *reports of epoxide hydrolases catalyzing epoxide-opening cyclization in polyether ionophore biosynthesis:* (a) Gallimore, A. R.; Stark, C. B. W.; Bhatt, A.; Harvey, B. M.; Demydchuk, Y.; Bolanos-Garcia, V.; Fowler, D. J.; Staunton, J.; Leadlay, P. F.; Spencer, J. B. *Chem. Biol.* **2006**, *13*, 453. (b) Shichijo, Y.; Migita, A.; Oguri, H.; Watanabe, M.; Tokiwano, T.; Watanabe, K.; Oikawa, H. *J. Am. Chem. Soc.* **2008**, *130*, 12230. (c) Matsuura, Y.; Shichijo, Y.; Minami, A.; Oguri, H.; Watanabe, M.; Tokiwano, T.; Watanabe, K.; Oikawa, H. *Org. Lett.* **2010**, *12*, 2226. (d) Smith, L.; Hong, H.; Spencer, J. B.; Leadlay, P. F. *ChemBioChem* **2008**, *9*, 2967. *review:* (e) Liu, T.; Cane, D. E.; Deng, Z. *Methods Enzymol.* **2009**, *459*, 187.

yields of the *endo* cyclization product. We ascribed this in part to the increased proclivity of trisubstituted epoxides to be protonated by trace hydronium and subsequently opened in unproductive pathways. Axial Me groups at ring junctions are potentially additionally problematic as they distort the plane of fused THP polycycles (see Chapter V). Neighboring ring junction Me groups are especially troublesome, as they incur severe 1,3-diaxial interactions. Forming such a substitution pattern via *endo* epoxide opening is extremely difficult, as evidenced by a thwarted cascade reported by Nicolaou[16] and by unpublished work from Dr. Denise A. Colby in the Jamison group.[17] Finally, proximal substitution, where the Me group is sited at the *exo* site of attack, is uniquely problematic (Scheme 1). Water-promoted cyclization onto these epoxides proceeds with relatively poor *endo* selectivity (**3** → **5**; see Chapter II). Moreover, the product of such cyclization is a tertiary alcohol, which would be expected to cyclize more slowly (e.g., **5** → **4**), thus allowing hydrolysis and other side reactions to compete.

[16] Nicolaou, K. C.; Seo, J. H.; Nakamura, T.; Aversa, R. J. *J. Am. Chem. Soc.* **2011**, *133*, 214.
[17] Colby, D. A.; Jamison, T. F. *Unpublished results.*

Scheme 1. Comparison of epoxide-opening cascades with and without a proximal Me group. Hypothesized stepwise mechanism from diepoxide **3** to THP triad **4**.



Of course, enzymatic catalysis could overcome all of the problems listed above. Enzymatic stabilization of the transition state to *endo* cyclization could engender superb *endo* cyclization in all circumstances, Me-substituted or not. While protected inside an enzymatic pocket, a delicate polyepoxide chain will not succumb to hydrolysis. In fact, the epoxide hydrolase Lsd19 identified by Oikawa and Leadlay very efficiently promotes *endo* cyclization of an epoxide with a challenging proximal substituent in the biosynthesis of the ionophore lasalocid.[15b,d] However, we are intrigued by an interesting pattern in the carbon sources of a few ladder polyethers, which suggests that Nature may be "aware" of the special problem of proximal Me substitution.

Dinoflagellates are notoriously difficult organisms to work with,[3d] and there have been but a few successful isotopic feeding studies. To the best of our knowledge, only three ladder polyethers have been subjected to feeding experiments with ^{13}C, to determine the origins of their carbon backbones. Those are brevetoxin A (BTX A, **6**),[18] brevetoxin B (BTX B, **8**),[18a,b] and yessotoxin (**10**).[19] All three structures contain a mixture of acetate Me-derived (m), acetate carbonyl-derived (c), and methionine-derived (M) carbons (Scheme 2). Remarkably, the methionine-derived carbons in all three natural

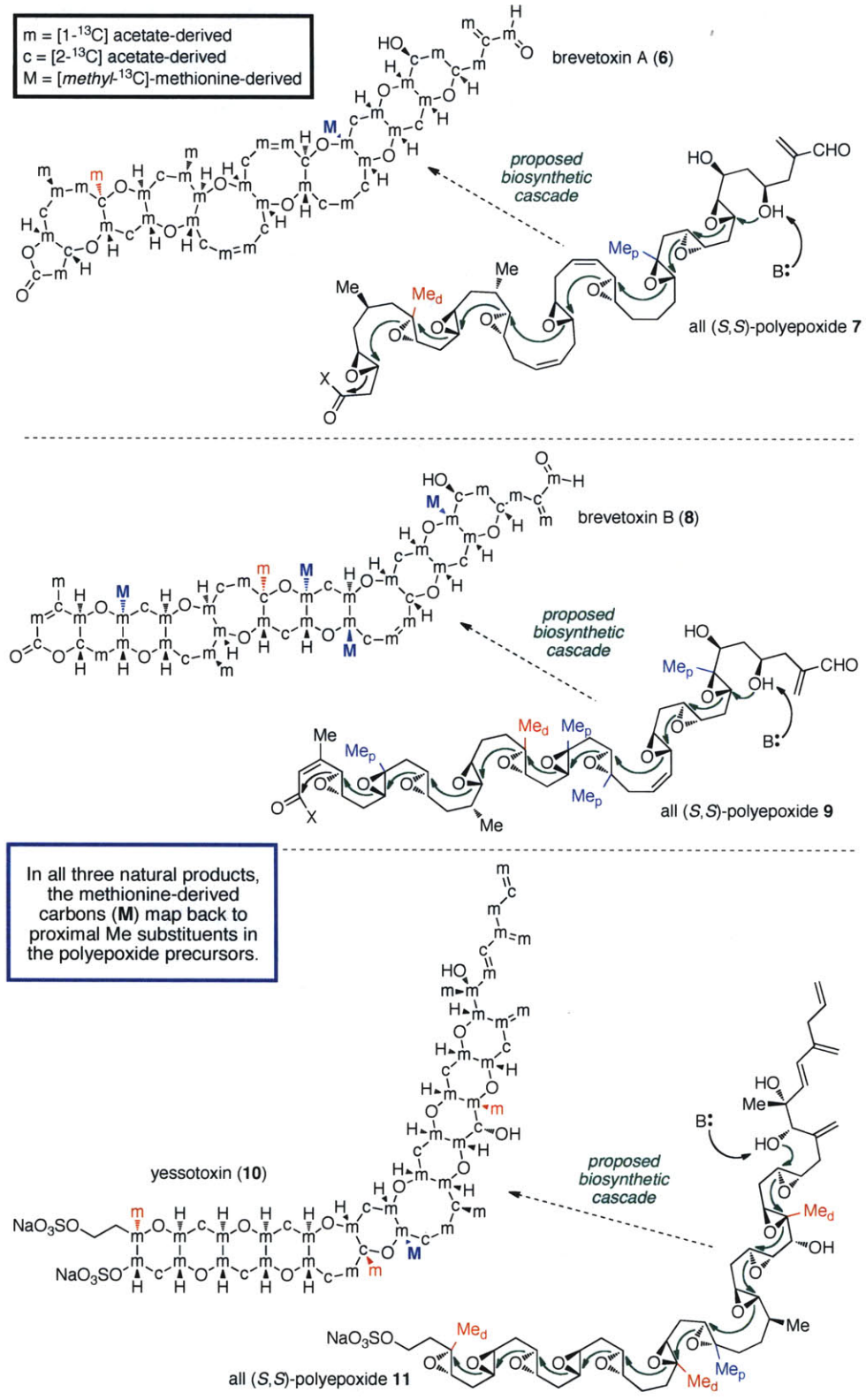
[18] (a) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855. (b) Lee, M. S.; Qin, G.-w.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234. (c) Chou, H.-N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184.

[19] Satake, M. *Symposium on the Chemistry of Natural Products (Japan)* **2000**, 42, 259.

products occur only as Me substituents at ring junctions. Equally striking, if one traces the natural products back to their likeliest immediate biosynthetic precursors, polyepoxide cascades substrates **7**, **9**, and **11**, all six of these methionine-derived carbons groups map to *proximal* Me substituents on their respective epoxides.[20] By contrast, the five ring junction Me groups in BTX A, BTX B, and yessotoxin that are acetate-derived all map to *distal* Me groups in the polyepoxide precursors. Three natural products is an admittedly small data set, but the trend exists.

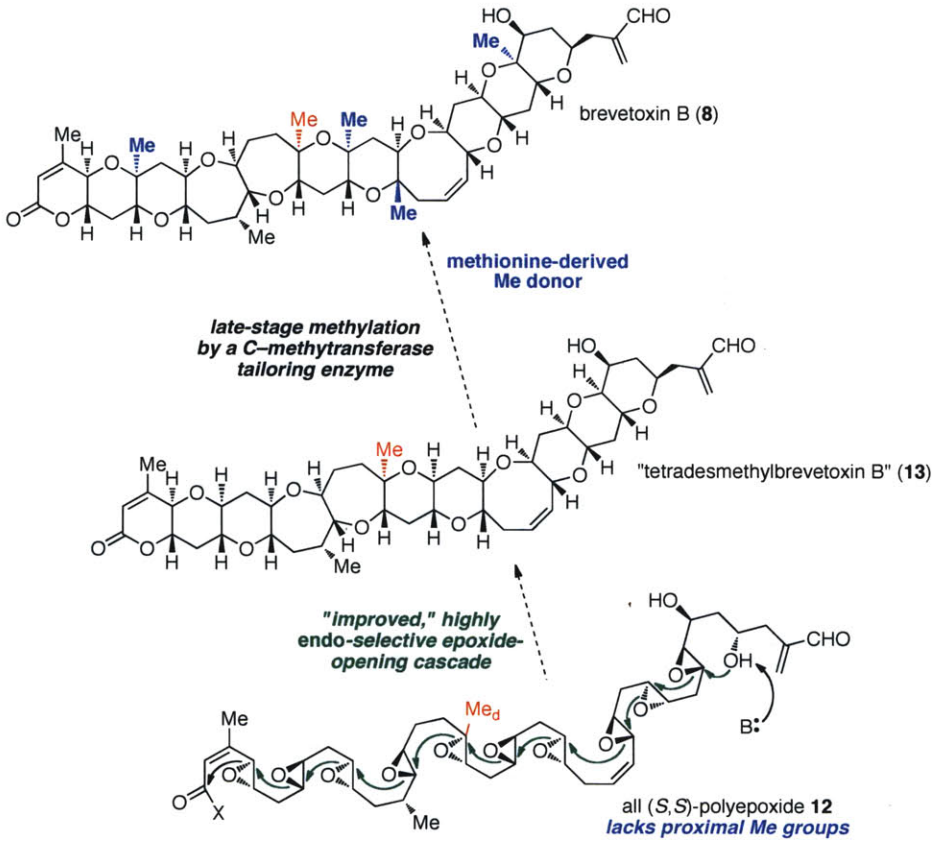
[20] In Scheme 2, we presume that each natural product is derived from the all-(*S*,*S*)-polyepoxide. It is conceivable that BTX A, BTX B, and yessotoxin could instead originate from all-(*R*,*R*)-polyepoxide precursors, via cascades that run in the opposite (left-to-right) direction. However, we suggest that the all-(*S*,*S*)-polyepoxides are the more likely precursors, as the right-to-left cascades shown conveniently account for the vicinal dioxygenation pattern observed at the left end of each ladder. (In the case of the brevetoxins, this vicinal dioxygenation pattern is "masked" in lactone rings.) This revealing pattern is a consistent clue to the probable direction of biogenetic cascades. On its basis, Wright and coworkers propose that all ladder polyethers produced by *Karenia brevis* arise from a conserved all-(*S*,*S*)-epoxidation pattern; see: (a) Satake, M.; Campbell, A.; Van Wagoner, R. M.; Bourdelais, A. J.; Jacocks, H.; Baden, D. G.; Wright, J. L. C. *J. Org. Chem.* **2009**, *74*, 989. (b) Van Wagoner, R. M.; Satake, M.; Bourdelais, A. J.; Baden, D. G.; Wright, J. L. C. *J. Nat. Prod.* **2010**, *73*, 1177.

Scheme 2. ^{13}C labeling patterns in brevetoxin A, brevetoxin B, and yessotoxin. Biosynthetic cascades to each, according to the prevailing hypothesis.



Given that the addition of proximal Me groups to epoxides undermines the efficiency of *endo*-selective epoxide-opening cascades, we are fascinated by the possibility that Nature might simply leave them out. Instead, the biosynthetic cascade could be executed without proximal Me groups (in presumably higher yield), and then the missing ring junction Me groups would be installed after the ladder is formed, using methionine as the carbon source (Scheme 3).

Scheme 3. Modified biosynthetic proposal for brevetoxin B. A cascade without proximal Me groups is followed by late-stage ring junction methylation.



We submit that such a proposal is not completely unreasonable, as a diverse set of downstream tailoring enzymes are known in polyketide biosynthesis, including enzymes catalyzing methylation.[21] There are several cases of methyltransferase tailoring enzymes

[21] (a) Walsh, C. T. *Science* **2004**, *303*, 1805. (b) Zhang, W.; Tang, Y. *Methods Enzymol.* **2009**, *459*, 367.

specifically promoting C–C bond formation.[22,23] Furthermore, *S*-adenosylmethionine (SAM) serves as Me donor in all of these examples, while the use of methionine as a carbon source in polyketide biosynthesis is otherwise fairly unusual.[24] In most cases of *C*-methylation by SAM (and indeed in the overwhelming of biological methyl transfer processes), it serves an electrophilic Me donor. For example, in the biosynthesis of the polyketide lovastatin, Me transfer occurs via simple nucleophilic attack by an enolate on SAM.[23,24a] However, in recent years much attention has been dedicated to the radical SAM superfamily of enzymes,[25] in which SAM acts not as electrophilic Me donor but rather as a precursor to the 5′-deoxyadenosyl radical, a versatile oxidant and powerful H$^{\bullet}$ abstractor capable of activating "unactivated" C–H bonds.[26] These enzymes are found in all kingdoms of life. Certain radical SAM enzymes have very recently been proposed to specifically catalyze radical methylation of relatively inert aromatic[22,27] and aliphatic C–H bonds.[28]

One instance of radical *C*-methylation in biosynthesis is reminiscent of the proposal in Scheme 3. The biogenesis of the antibiotic fosfomycin (**23**) is proposed to involve late stage C–H bond activation by a radical SAM enzyme and subsequent radical methylation (Scheme 4).[28b,c] Radical SAM enzyme Fom3 generates 5'-deoxyadenosyl radical **16**, which abstracts a hydrogen atom from hydroxyethylphosphonate (HEP, **18**). The particular H atom abstracted is on a carbon bound to an oxygen, which stabilizes the

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[22] Lozano, M. J. F.; Remsing, L. L.; Quiros, L. M.; Brana, A. F.; Fernandez, E.; Sanchez, C.; Mendez, C.; Rohr, J.; Salas, J. A. *J. Biol. Chem.* **2000**, *275*, 3065.

[23] (a) Moore, R. N.; Bigam, G.; Chan, J. K.; Hogg, A. M.; Nakashima, T. T.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 3694. (b) Kennedy, J.; Auclair, K.; Kendrew, S. G.; Park, C.; Vederas, J. C.; Hutchinson, C. R. *Science* **1999**, *284*, 1368.

[24] *general reviews of polyketide biosynthesis:* (a) Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380. (b) Fischbach, M. A.; Walsh, C. T. *Chem. Rev.* **2006**, *106*, 3468. (c) Hertweck, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4688.

[25] Sofia, H. J.; Chen, G.; Hetzler, B. G.; Reyes-Spindola, J. F.; Miller, N. E. *Nucleic Acids Res.* **2001**, *29*, 1097.

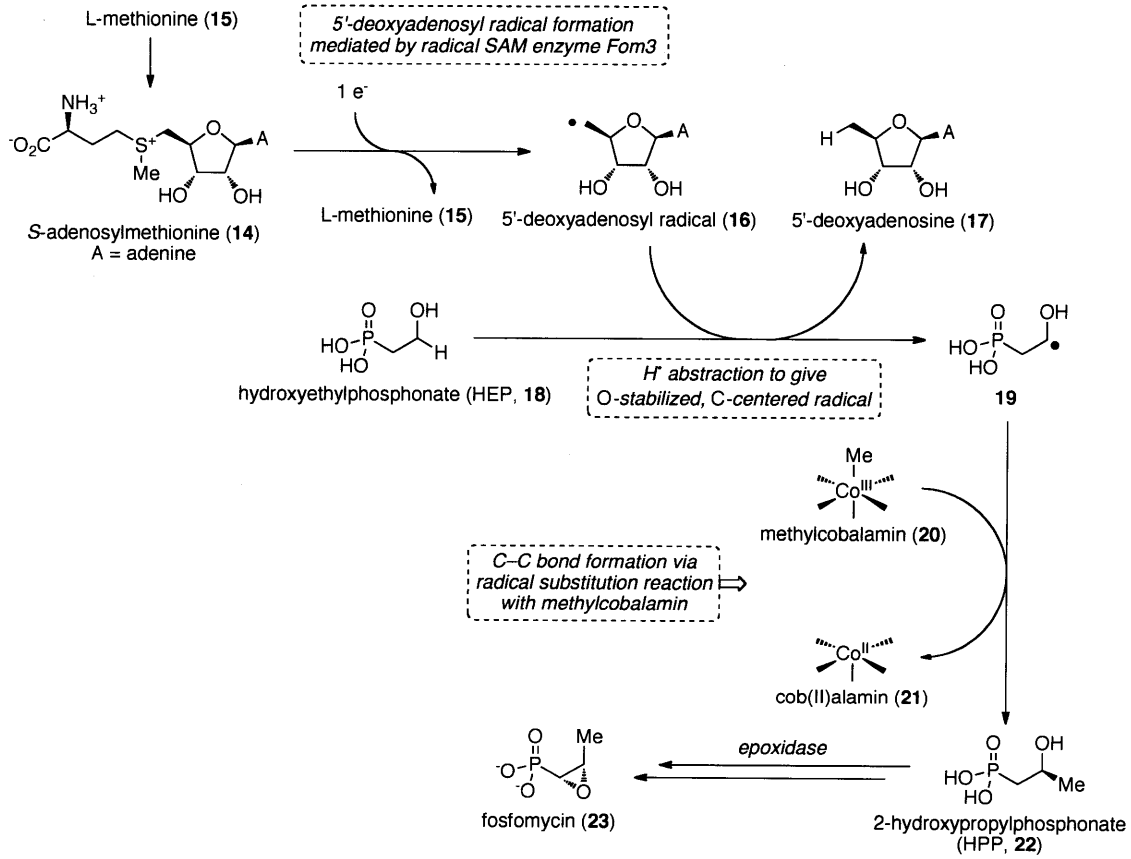
[26] (a) Booker, S. J. *Curr. Opin. Chem. Biol.* **2009**, *13*, 58. (b) Booker, S. J.; Grove, T. L. *F1000 Biol. Rep.* **2010**, *2*:(52). (c) Wang, S. C.; Frey, P. A. *Trends Biochem. Sci.* **2007**, *32*, 101.

[27] (a) Yan, F.; LaMarre, J. M.; Röhrich, R.; Wiesner, J.; Jomaa, H.; Mankin, A. S.; Fujimori, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 3953. (b) Yan, F.; Fujimori, D. G. *Proc. Nat. Acad. Sci.* **2011**, *108*, 3930. (c) Grove, T. L.; Benner, J. S.; Radle, M. I.; Ahlum, J. H.; Landgraf, B. J.; Krebs, C.; Booker, S. J. *Science* **2011**, *in press* [DOI:10.1126/science.1200877].

[28] (a) Kuzuyama, T.; Seki, T.; Dairi, T.; Hidaka, T.; Seto, H. *J. Antibiot.* **1995**, *48*, 1191. (b) van der Donk, W. A. *J. Org. Chem.* **2006**, *71*, 9561. (c) Woodyer, R. D.; Li, G.; Zhao, H.; van der Donk, W. A. *Chem. Commun.* **2007**, 359.

resulting *C*-centered radical **19** by about 3 kcal/mol.[29] Organic radical **19** then reacts with Me group of methylcobalamin (**20**)[30] to generate 2-hydroxypropylphosphonate (HPP, **22**).

Scheme 4. Proposed biosynthesis of fosfomycin. (van der Donk, ref. 28b,c. Redox steps required to regenerate methylcobalamin and the active form of Fom3 are unknown and not shown.)



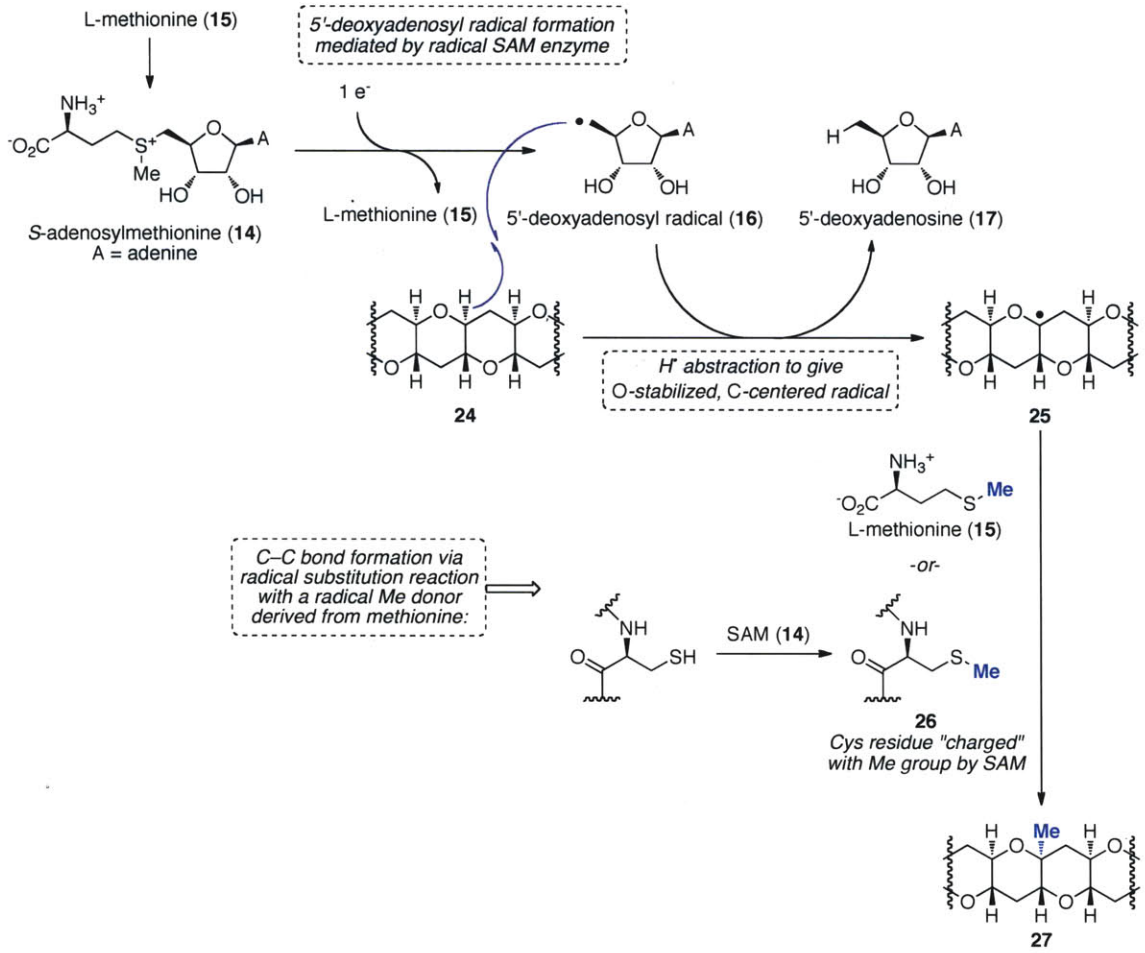
A similar mechanism can be conceived for radical methylation of ladder polyethers (Scheme 5). An axial ring junction hydrogen atom of ladder polyether **24** could be abstracted by 5'-deoxadenosyl radical **16** to give the *O*-stabilized radical **25**. Radical **25** would then be quenched by a methyl donor to give substituted ladder **26**. Obviously, to account for the methionine-derived Me groups of yessotoxin and the brevetoxins, the species that donates a Me group to **25** must be methionine or

[29] (a) McMillen, D. F.; Golden, D. M. *Ann. Rev. Phys. Chem.* **1982**, *33*, 493. (b) Lao, Y.-R. *Comprehensive Handbook of Chemical Bond Energies*; CRC Press: Boca Raton, 2007.
[30] Mosimann, H.; Kräutler, B. *Angew. Chem. Int. Ed.* **2000**, *39*, 393.

methionine-derived; it cannot be methylcobalamin (**20**), used in fosfomycin biosynthesis. We leave the last step of our hypothesis intentionally indistinct, as the mechanism of Me donation in radical SAM-mediated processes is unknown and currently a topic of significant debate.[26,27,28b] Fujimori originally proposed that SAM itself could act as a radical Me donor,[27a] but later deemphasized this proposition on the basis of labeling experiments and bond dissociation energies.[27b] Very recently, Booker revealed that the Me donor may not be SAM or methionine themselves but rather a cysteine residue to which a Me group has been transferred by SAM.[27c] We posit that methionine (**15**) or a methylated cysteine residue (**26**) are plausible Me donors in the final step, as in either case the Me transfer would generate a relatively stable sulfenyl radical.[31]

[31] Armstrong, D. A. Thermochemistry of Sulfur Radicals. In *S-Centered Radicals*; Alfassi, Z. B., Ed.; John Wiley & Sons: West Sussex, UK, 1999; p. 27.

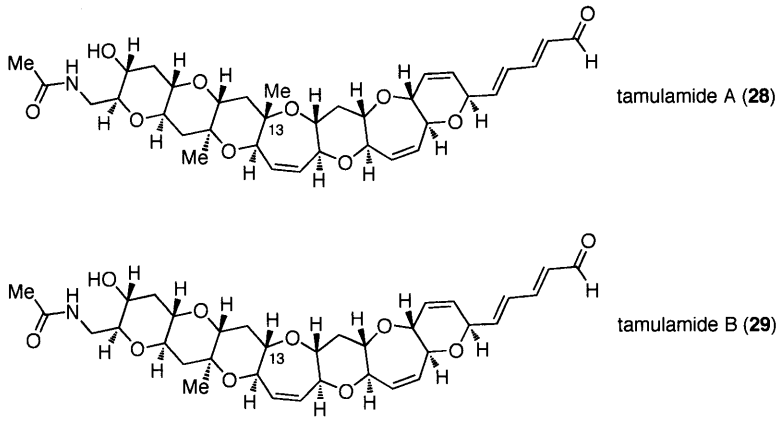
Scheme 5. Proposed late-stage methylation of fused ladder polyether structures.



The recent characterization of two new ladder polyether structures offers additional, if highly circumstantial, evidence for the possibility of late-stage methylation. Tamulamides A and B were isolated by Bourdelais from *Karenia brevis*, the same dinoflagellate species that produces the brevetoxins.[32] These natural products differ only by the presence or absence of a single axial Me group sited at an interior ring junction (Figure 1). It is tempting to speculate that desmethylated tamulamide B (**29**) could be a biosynthetic precursor to tamulamide A (**28**).[33] However, labeling studies of the tamulamides have not yet been reported, and it is unknown whether the pertinent C_{13} Me substituent is methionine-derived.

[32] Truxal, L. T.; Bourdelais, A. J.; Jacocks, H.; Abraham, W. M.; Baden, D. G. *J. Nat. Prod.* **2010**, *73*, 536.
[33] We must acknowledge that the methylated tamulamide A appears to have *lower* binding affinity for voltage-gated sodium ion transport channels and lower overall bioactivity then desmethylated tamulamide B, which undermines the notion that Nature affixes the C_{13} Me group to improve binding; see ref. 32.

Figure 1. Recently reported structures of the tamulamides.



If indeed Nature installs ring junction methyl substituents after and not before epoxide-opening cascades, it is unclear what recognition elements the relevant tailoring enzymes might use to determine which ring junctions to methylate. There is no clear pattern among BTX A, BTX B, and yessotoxin (**6**, **8**, and **10**, Scheme 2); that is, methionine-derived axial Me groups variously appear at 6,6, 6,7, and 6,8-fused ring junctions in the three compounds, and we are unable to identify any more subtle organization.

In conclusion, it is likely that any *endo*-selective epoxide-opening cascades in the biosynthesis of the ladder polyethers is enzymatically controlled. Still, lessons learned from the study of epoxide-opening cyclization promoted by water may bear on the biogenetic puzzle. We are particularly intrigued by the possibility that Nature may sidestep the incorporation of certain methyl groups into the polyepoxide substrates for biogenetic cascades. Rather than engineer challenging cascades containing proximally Me-substituted epoxides and/or potential 1,3-diaxial interactions, Nature may wait until after the cascade to install the Me groups in question. Such post-cascade modification via tailoring enzymes would provide a general and versatile strategy for the methylation of ring junctions. In turn, the decoration of even a single ring junction with a Me group can engender significant changes in the conformation and consequent bioactivity of the natural product[34] — axial Me substituents are proposed to insulate the unpaired electrons

[34] For analyses of how minor changes to ladder polyether structure can have a profound impact on bioactivity, please see: (a) Rein, K. S.; Lynn, B.; Gawley, R. E.; Baden, D. G.*J. Org. Chem.* **1994**, *59*,

of neighboring oxygen atoms and improve lipophilicity.[35] "Tetradesmethylbrevetoxin B" (**13**, Scheme 3) is not a known compound, nor likely to be a simple one to prepare, but we are fascinated by the possibility that it could be a intermediate en route to brevetoxin B.

2107. (b) Gawley, R. E.; Rein, K. S.; Jeglitsch, G.; Adams, D. J.; Theodorakis, E. A.; Tiebes, J; Nicolaou, K. C.; Baden, D. G. *Chem. Biol.* **1995**, *2*, 533.

[35] Torikai, K,; Oishi, T.; Ujihara, S.; Matsumori, N.; Konoki, K.; Murata, M.; Aimoto, S.*J. Am. Chem. Soc.* **2008**, *130*, 10217.

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2003-2005: **teaching assistant** for Introduction to College Chemistry, General Chemistry, and Organic Chemistry Lab, Columbia U.

Awards and Distinctions

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2010 Roche Excellence in Chemistry Award
2010 MIT Pfizer Scholar Award
2010 MIT Morse Travel Grant
2009 Merck Summer Fellowship
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2007 Outstanding Teaching Award, MIT Chemistry Department
2005 Brian Bent Award for excellence in teaching, Columbia Chemistry Department
2005 election to Phi Beta Kappa

Publications

Morten, C. J.; Jamison, T. F. "Water Overcomes Methyl Group Directing Effects in Epoxide-Opening Cascades," *J. Am. Chem. Soc.*, **2009**, *131*, 6678-6679.

Morten, C. J.; Jamison, T. F. "New Synthetic Strategies for the Stereocontrolled Synthesis of Substituted 'Skipped' Diepoxides," *Tetrahedron Symposium-in-Print*: 2008 Tetrahedron Prize for Creativity in Organic Chemistry to Professor Larry E. Overman, *Tetrahedron* **2009**, *65*, 6648-6655.

Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. "The Development of Endo-Selective Epoxide-Opening Cascades in Water," *Chem. Soc. Rev.* **2009**, *38*, 3175-3192.

Morten, C. J.; Byers, J. A.; Jamison, T. F. "Evidence that Epoxide-Opening Cascades Promoted by Water Are Stepwise and Become More Selective After the First Cyclization," *J. Am. Chem. Soc.* **2011**, *133*, 1902-1908.